

American Journal of
DIGESTIVE DISEASES
Volume 10

duced the world's food supply, affected consumption in almost every country, and led to scarcity and famine in countries occupied by the enemy. The task of producing enough food to meet the needs of the United Nations and to feed countries at present starving in bondage is a formidable one, which, as recovery from the war takes place, will merge into the broader problem of increasing production and raising consumption throughout the world as a whole. While the present report is not concerned directly with the existing situation and post-war relief, it is clear that the acute and immediate problem and the long-term problem are in many respects parallel, each calling urgently for concerted action.

Malnutrition leads to ill-health and disease and must, therefore, be eliminated. But there is a more positive goal which should never be lost to view. Good food means good health. It enhances the capacity of human beings to contribute to civilization and progress, and adds to human happiness. Given the will, we have the power to build in every nation a people more fit, more vigorous, more competent, a people with longer, more productive lives, and with more physical and mental stamina than the world has ever known. Such prospects remote though they may be, should serve as a stimulus in undertaking immediate tasks and overcoming immediate obstacles.

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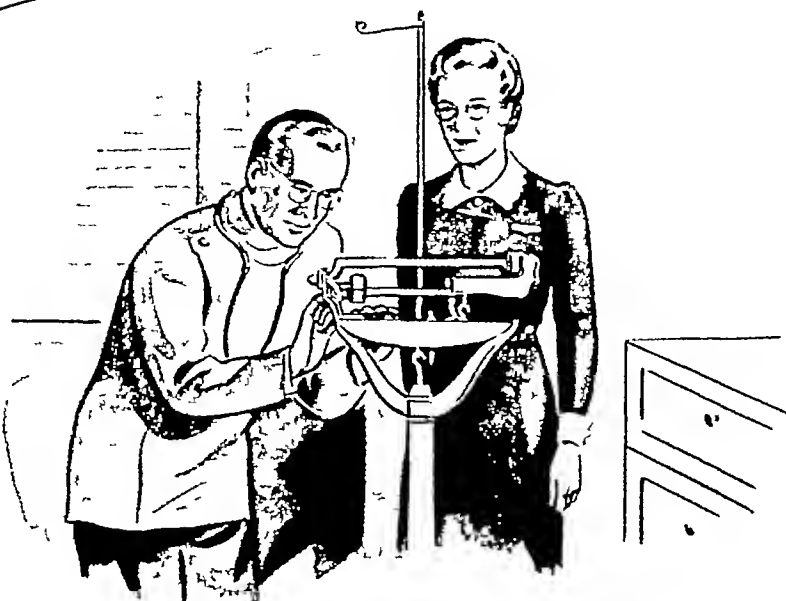
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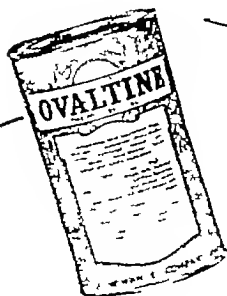
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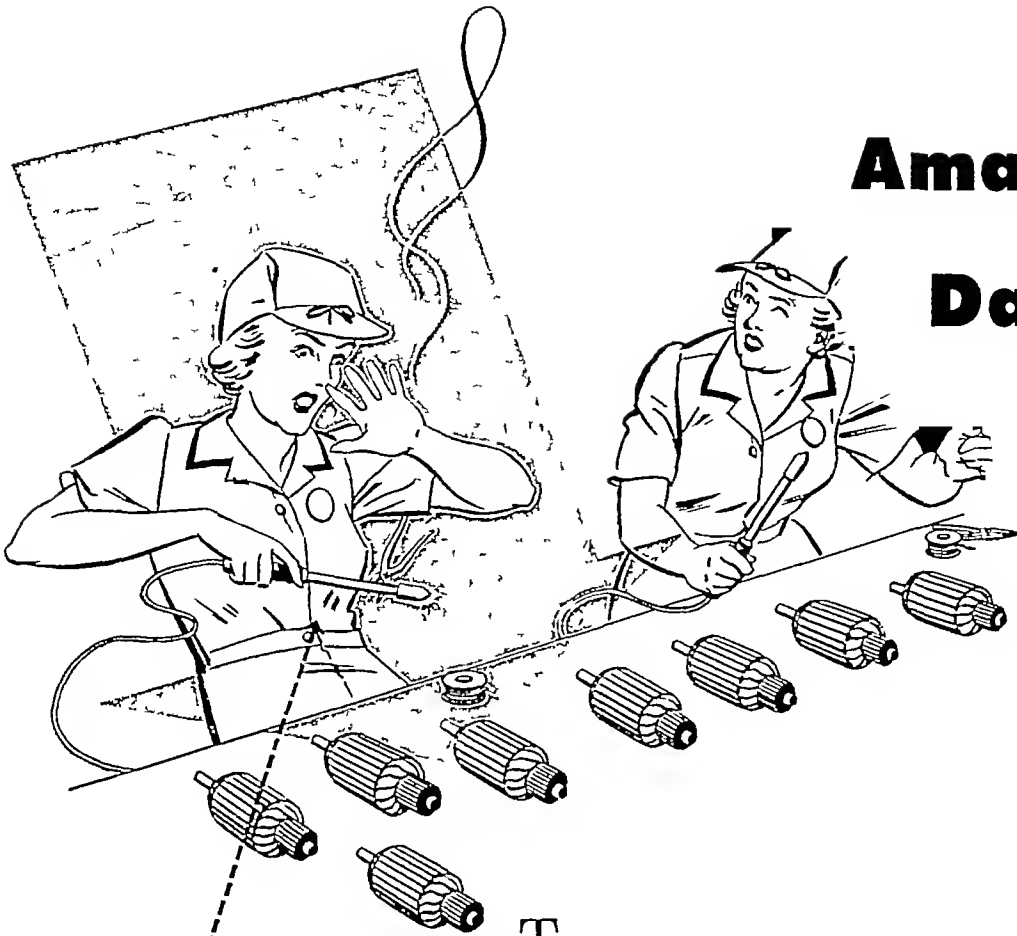


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IRON	10.5 mg.	11.94 mg.	COPPER	.5 mg.	.5 mg.

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The Present Status of the Serum Lipase Test*

By

THOS A JOHNSON, M D

and

H L BOCKUS, M D

PHILADELPHIA PENNSYLVANIA

IN 1940 we (1) reported a series of 616 serum lipase determinations on 371 patients. Our present series, including those previously reported, comprises 1200 determinations on 800 patients. The cases were studied over a period of six years. An analysis of this larger group of cases has served to confirm the opinion previously expressed concerning the specificity of hyperlipasemia in pancreatic disease (1). Other investigators concur in those conclusions (2, 3, 4, 5).

The technic of the serum lipase test has been described (1, 6). The results of the test are expressed in terms of cubic centimeters of one-twentieth normal sodium hydroxide. Normal values range below 1.0 cc. Abnormal values range from 1.0 to 10.0 cc.

Various explanations have been offered to account for elevated serum lipase values. We believe that any mechanism which blocks one or more of the larger pancreatic ducts may cause an increase in the concentration of the serum lipase because of absorption of that ferment into the blood stream. Hyperlipasemia of obstructive origin has been reported in the following conditions: (1) Experimental ligation of one or more of the larger pancreatic ducts; (2) Edema of the pancreas or surrounding structures secondary to inflammatory changes; (3) Pressure of a tumor arising in or near the pancreas. Such pressure may be exerted by enlargement of lymph nodes near the head of the pancreas; (4) Pancreatic lithiasis in which a stone blocks one of the pancreatic ducts.

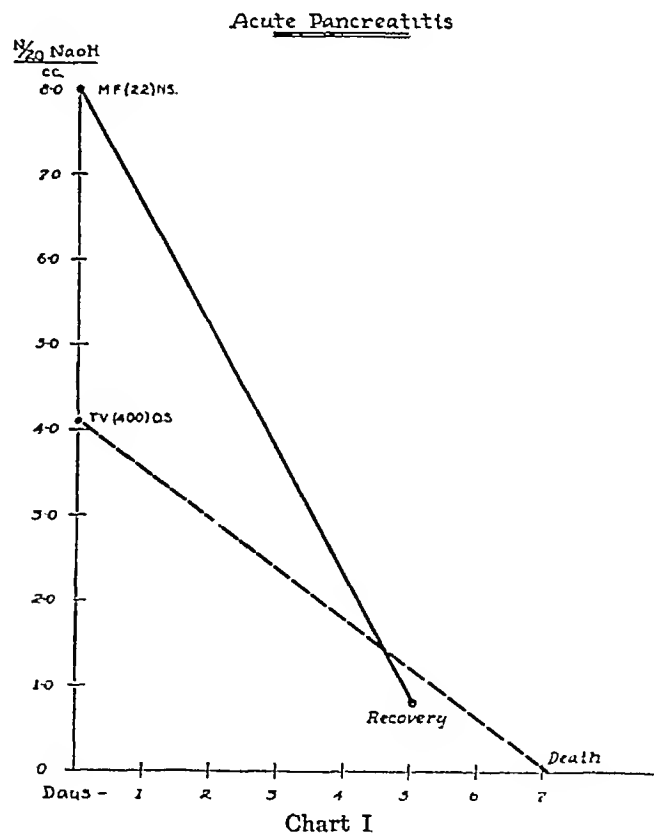
Some writers believe that the absorption of pancreatic debris secondary to acute necrosis of the pancreas may cause an increase in the serum lipase activity. Our data are insufficient to afford any reasonably accurate opinion concerning that observation.

Having been convinced of the specificity of hyperlipasemia in pancreatic disease it was decided to utilize this extensive material to study the behavior of this enzyme in the serum throughout the course of certain proved cases of pancreatic disease. Repeated determinations during the course of the disease have thrown further light upon the mechanism of hyperlipasemia and added to our knowledge of the clinical value of the test. Simultaneous bromsulphthalein liver function tests were frequently available and the serum bilirubin concentrations were of assistance in estimating the degree of biliary obstruction in many instances. The cases utilized for discussion were segregated from 21 cases of acute pancreatitis, one case of chronic pancreatitis and 30 cases of pancreatic cancer. The serum lipase value was above 1.0 cc at least once during the course of the illness in 17 cases

(81%) of acute pancreatitis and in 16 cases (53.3%) of cancer of the pancreas.

ACUTE PANCREATITIS

Chart I indicates the range of serum lipase concentrations in two cases of acute pancreatitis. Case M F, with a maximum serum lipase value of 8.0 cc and a normal serum lipase on the fifth day, probably represented an acute transient pancreatitis. The patient improved with conservative management. Some operative objective finding might have added force to our case presentation, however, she presented a typical



clinical picture of acute transient pancreatitis (7). Case T V, with a serum lipase only half as high as Case M F, died and autopsy disclosed a completely necrotic pancreas. These cases illustrate several features of the serum lipase determination: (1) The height of the serum lipase value is not an accurate prognostic sign; (2) A drop to normal may be due to a subsiding inflammation or it may indicate complete necrosis of the pancreas. Case T V did not support the validity of the concept that absorption of necrotic pancreatic debris might give rise to an elevated serum lipase; (3) In cases of suspected acute pancreatitis

*From the Gastro-Intestinal Service of the Graduate Hospital of the University of Pennsylvania.

Read at the Annual Meeting of the American Gastro-Enterological Association at Atlantic City, N. J., June 29, 1942.

the serum lipase must be interpreted in terms of the clinical condition of the patient. A single determination on Case T V just prior to death failed to suggest any pancreatic abnormality unless the very low reading (0.06) may be looked upon as an indication of almost complete suppression of pancreatic function. The second test on Case M F gave no indication of the event that occurred five days previously.

In the case protocols which follow, the blood sugar and serum bilirubin determinations are reported in terms of milligrams per 100 cubic centimeters of blood, the serum lipase in terms of cubic centimeters of one-twentieth normal sodium hydroxide, the bromsulphthalein in terms of per cent retention in 30 minutes of the dye following an injection of 2 milligrams per kilogram of body weight.

Case T V, an Italian female, 48 years of age, was admitted August 1, 1938, to the Graduate Hospital on the Gynecology Service because of vaginal bleeding. Her first attack of abdominal pain occurred in 1923, lasting 12 hours. No pain occurred subsequently until two weeks prior to the present admission. On August 1, 1938, she developed severe generalized abdominal pain in association with vomiting. The history is not clear concerning the relationship of the abdominal pain to the vaginal bleeding. On admission the temperature and pulse were elevated, the abdomen was rigid and tympanic. The fasting blood sugar was 366 mg. The serum lipase was 4.18 on August 3, 1938. There was a surgical opinion on admission to the hospital to the effect that the patient was suffering from generalized peritonitis probably secondary to an acute appendicitis. The Gastro-Intestinal Service was not consulted. On August 10, 1938, the leucocyte count was 20,000 with 84 per cent polymorphonuclear cells. The routine serologic tests for syphilis were positive. On August 11, 1938, the serum lipase was 0.06. The patient expired that day. Autopsy disclosed acute hemorrhagic pancreatitis with almost complete necrosis of the pancreas.

Case M F, a white female, 50 years of age, was first seen by one of us on January 25, 1940. In 1935 and 1936 there had been a series of attacks of severe upper abdominal pain often requiring hypodermic medication for relief. No jaundice was noted. The present episode began early in December, 1939, with severe epigastric pain referred to the interscapular region for which a hypodermic was required. Similar attacks recurred approximately every other day. The most recent attack started at 1 a. m. on January 25, 1940, and for the first time jaundice was noted in association with dark urine. Nausea and vomiting were present. The pain for the first time tended to radiate not only to the interscapular region but toward the left upper quadrant. The morning temperature on January 25, 1940 was normal but increased to 100 degrees later in the day. Thereafter the patient was afebrile. On January 25, 1940 the leucocyte count was 6600 with 80 per cent polymorphonuclear cells, the serum bilirubin was 1.5 and the serum lipase 8.0. The patient was admitted to the Graduate Hospital on January 25, 1940 where she remained for 7 days. Her symptoms subsided on January 26, 1940 and she remained free from pain thereafter. The sugar tolerance test was normal three days after admission. An intravenous cholecystogram showed a non-functioning gall bladder. A diagnosis of possible biliary colic with transient acute pancreatitis was made. Five days later the serum lipase was 0.8. The patient refused operation and was returned to her referring physician for follow up. At the present time (May, 1942) the patient's physician states that she continues to suffer from attacks of severe upper abdominal pain requiring hypodermic medication for relief. She refuses surgical intervention.

Chart II represents three cases of acute pancreatitis confirmed by operation. In case R B the highest

serum lipase value was obtained at the time of admission 48 hours after the onset of an attack of acute cholecystitis. The concentration of lipase remained high during the 12 day "cooling off period" before operation and persisted until the time of her discharge one month after operation. A T-tube was in situ during this time. Evidently some degree either of pancreatic duct obstruction or inflammation of the pancreas persisted up to the time of discharge.

The serum lipase curve in case M S seems closely related to the clinical and pathologic features of the case and requires no further comment.

In case G C it is probable that the first serum lipase determination was not made until 3 weeks after the pancreatic insult. This may account for the comparatively slight rise in lipase at that time. The secondary rise in the serum lipase value may represent the occurrence of a second minor pancreatic insult.

Case R B, a negress, 44 years of age, was admitted to the Gastro-Intestinal Service of the Graduate Hospital on June 4, 1940, with chills, fever and abdominal pain. The past history was irrelevant. She had complained of flatulent dyspepsia for many years. Four months before admission she had an attack of severe abdominal pain. The present attack began 48 hours before admission, centering in the upper right quadrant and radiating to the right dorsal spine. Dark brown urine was noted. On admission to the ward the patient was afebrile but soon developed a moderate fever. There was tenderness and muscle guarding in the gall bladder area. The tentative diagnosis was acute cholecystitis with pancreatitis. Conservative initial treatment was adopted. On June 17, 1940, Dr. W. E. Lee performed a cholecystectomy. The common duct was filled with stones. The pancreas felt normal to the palpating hand. A T-tube was placed in the common bile duct. The patient was discharged to her family doctor on August 2, 1940. The following pertinent laboratory data were recorded:

Date	Serum Lipase	Serum Bilirubin	Blood Sugar
5-5-40	5.90	1.5	142
6-6-40		"	96
5-7-40			95
6-8-40		4	
6-10-40	2.50		
6-11-40		.2	
6-12-40	2.40		
6-13-40	2.40		
6-17-40			
Operation	2.20		
6-18-40	0.87	7	
6-21-40	1.20		
6-24-40	2.10		
6-27-40	2.20		
" 1-30	2.10	.5	
" 3-40	2.80		
" 6-40	1.90	.3	
7-16-40	1.80		

Case M S, a negress, 39 years of age, was admitted to the Gastro-Intestinal Service of the Graduate Hospital on June 9, 1940, complaining of severe abdominal pain. For 10 years previous to admission the patient had suffered from recurrent attacks of upper abdominal pain. One year before admission bile drainage showed calcium bilirubinate and cholesterol crystals. One month before admission the cholecystogram in the out-patient department showed cholelithiasis. During the two weeks immediately preceding admission she complained of daily epigastric pain and tenderness. On admission the temperature was 99.6 degrees, pulse 102, leucocytes 19,000 with 93 per cent

polymorphonuclear cells blood sugar 125 On the day after admission a tender smooth mass about 4 inches in diameter could be palpated in the epigastrium Later the mass became smaller and on June 28, 1940, was about 2 inches in diameter A barium enema roentgen study indicated that an extrinsic mass in the upper abdomen was pressing on the mid transverse colon On July 1, 1940, (21 days after admission) Dr W E Lee removed the gall bladder which was filled with stones A pancreatic cyst was found involving the head of the pancreas The cyst was opened and 70 cc of thick, dark reddish-brown fluid was evacuated The cyst was thought to be secondary to an inflammatory necrotic lesion of the pancreas The cyst was marsupialized On August 2, 1940 the patient was discharged after an uneventful recovery The pertinent laboratory data follows

Date	Serum Lipase	Serum Bilirubin	Blood Sugar
6-10-40	3.70	1.0	125
6-11-40			88
6-12-40	2.90	0.4	
6-17-40	1.50	0.2	
6-19-40	1.70		
6-22-40	1.50	0.2	
6-24-40	1.60		
6-27-40	0.80	0.2	
7-1-40 Operation			
7-2-40	0.80		
7-13-40	0.60	0.2	
7-22-40	0.20		
7-24-40	0.32		

Case G C, a white male, 42 years of age, was admitted to the Graduate Hospital on September 23, 1937 For 8 years prior to admission he had suffered from attacks of severe upper abdominal pain coming on every 1 or 2 months and requiring hypodermics of morphine for relief During the three weeks prior to admission he noted some pain each day in the epigastrium which radiated to the left costal margin and interscapular regions There had been a recent loss of weight from 167 to 134 pounds The past medical history was irrelevant except for typhoid fever Physical examination was not noteworthy except for the presence of jaundice On October 14, 1937, Dr Wm Bates operated The gall bladder was distended and edematous No stones were found A mass was present behind the first portion of the duodenum, containing some cheesy material, and representing the residual effect of

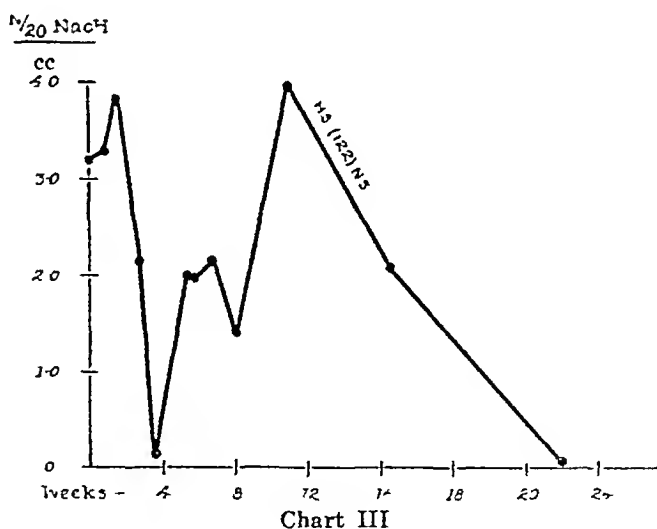
inflammation of the head of the pancreas The condition of the gall bladder precluded an anastomotic operation Cholecystostomy was performed The patient had a stormy convalescence complicated by a bile fistula which closed spontaneously He subsequently developed severe diabetes which required standardization When last observed in August, 1939, he complained of no symptoms referable to the biliary tract The pertinent laboratory data follow

Date	Serum Lipase	Serum Bilirubin	Bromsulphthalein Per Cent Retention
9-25-37	1.20	6.0	15
9-28-37	0.25	6.0	65
10-2-37	0.94	4.0	35
10-4-37		3.0	
10-9-37	0.56	6.0	55
10-14-37 Operation			
10-20-37		1.5	
10-27-37		1.0	
11-1-37		0.2	
11-4-37		0.6	
11-9-37	0.95	0.6	
11-16-37	0.78	0.4	
11-30-37	2.80	0.3	
12-4-37	1.80		
4-19-38	0.18		
2-10-39	0.80		
3-4-39	0.42		

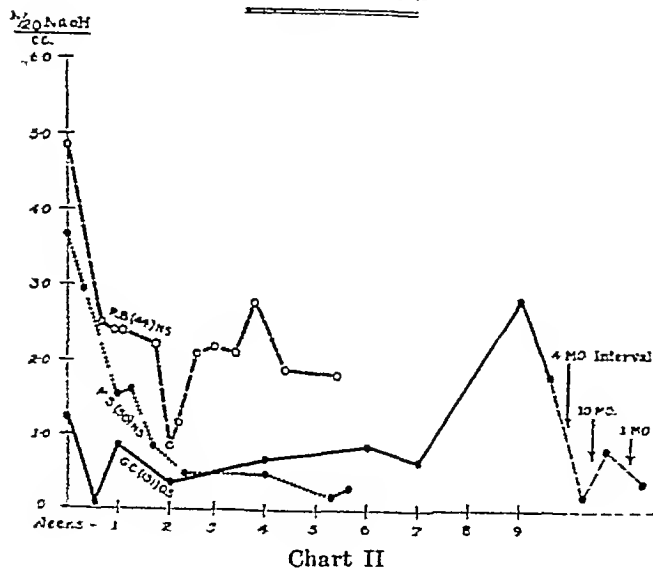
CHRONIC PANCREATITIS

Chart III represents a case of chronic interstitial pancreatitis, a diagnosis which we made with some reluctance, but which seemed supported by adequate biopsy and clinical data Case H S is the only one

Chronic Pancreatitis



Acute Pancreatitis



so diagnosed in our series The initial clinical and surgical picture could not be distinguished from that of malignancy of the pancreas The progressive elevation of the serum bilirubin seemed to favor a malignant obstruction of the biliary tract, and in conjunction with the elevated serum lipase, favored a diagnosis of malignancy in or near the ampulla of Vater At operation Dr W E Lee found an enlarged head of the pancreas from which a section was removed for biopsy Dr E Case made a microscopic diagnosis of chronic interstitial pancreatitis Cholecystojejunostomy relieved the jaundice At the time

of this report (18 months from the time of his admission to the Graduate Hospital) he remains well. Both the obstructive jaundice and the elevated serum lipase seemed to have been the result of pressure on the ampulla of Vater and adjacent regions from edema secondary to the inflammatory process. The serum lipase curve of case H S on Chart III does not differ materially from the curves of malignant disease of the pancreas illustrated in Chart IV. Except for a single post-operative determination a normal serum lipase value was not obtained until more than 4 months following operation. The case protocol follows:

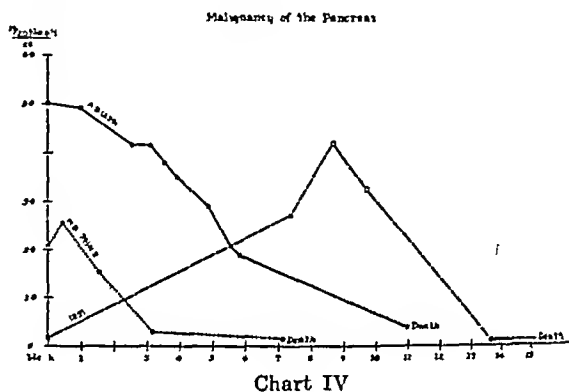
Case H S, a white male, 56 years of age, with a long history of bronchial asthma, entered the Graduate Hospital with clinical jaundice on January 27, 1941. For 9 years he had noted occasional upper right quadrant distress. Five weeks prior to admission he had had an acute upper respiratory infection with some increase in upper right quadrant pain which radiated to the back. On admission the temperature, pulse and respiration were normal. There was slight muscle guarding in the upper right quadrant. The gall bladder was not palpable. From admission to February 21, 1941, there was a progressive increase in the jaundice. The bromsulphthalein test showed 80% retention in 30 minutes on February 8, 1941. On February 21, 1941, under spinal anaesthesia the common bile duct was explored. No stones were found. There was a complete block of the distal common duct due to an enlarged pancreas. A cholecystojejunostomy was performed. A T-tube was inserted into the common duct for external drainage of bile. A biopsy from the pancreas was reported "chronic interstitial pancreatitis" with no evidence of malignancy. On March 25, 1941, the serum bilirubin was 0.7 and the bromsulphthalein showed only 6 per cent retention. After an uneventful recovery the patient was discharged on April 1, 1941, with the T-tube still in place. On June 24, 1941, a cholangiogram showed the common duct still blocked at the site of the pancreas. The cholecystojejunostomy functioned adequately. The patient has been well since discharge without any recurrence of jaundice. The following pertinent laboratory data were recorded:

Date	Serum Lipase	Serum Bilirubin	Bromsulphthalein Per Cent Retention
1-29-41	3.20	2.0	
2-1-41		4.0	60
2-1-41	3.30	4.0	75
2-6-41	3.80		
2-11-41		4.8	80
2-15-41	2.20	5.0	60
2-21-41		6.0	
Operation		1.5	
2-24-41		6.5	
2-28-41		5.0	
3-4-41		6.0	
3-10-41	2.00	9.5	
3-18-41	2.00	5.2	
3-10-41		4.5	
3-13-41		2.7	
3-15-41	2.20		
3-17-41		1.5	
3-21-41	1.42	0.7	6
4-12-41	3.92	0.2	5
4-13-41	2.20	0.2	0
7-1-41	0.07	0.2	0

MALIGNANCY OF THE PANCREAS

Chart IV represents 3 cases of malignancy of the pancreas which were followed to the time of death. In each case an anastomosis of the gall bladder to the stomach or jejunum was made to relieve the jaundice.

Case A B showed a progressive decrease in the serum lipase values and the last determination, shortly before death, fell within the normal range. We believe that the gradual replacement of functioning pancreatic tissue by malignant tissue accounted for the above change which took place after the initial blocking of one of the main pancreatic ducts by the growth. The decrease in lipase values might likewise be explained on the basis of pancreatic exhaustion from long continued obstruction in a fashion analogous to that type of hepatic exhaustion following prolonged common duct obstruction. It is significant that a normal lipase value was present in each of the three cases some time before death and a normal value was obtained initially in case A L. An analysis of the serum lipase curves in conjunction with the case records suggests that isolated normal serum lipase values are of no significance in ruling out the presence of pancreatic malignancy. The pancreas may be so extensively involved when the case is first seen that the



lipase determination will be within or below the normal range. In other cases of pancreatic malignancy death may occur before the malignant process has progressed sufficiently to cause obstruction of a main pancreatic duct. The case protocols follow:

Case A B, a 55 year-old colored male, was first treated as a case of duodenal ulcer (hospitalization from Dec. 30, 1937, to Jan. 24, 1938, because of ulcer like symptoms) although no niche was seen on the X-ray films. At that time the blood sugar was normal and no serum lipase was ordered. He was re-admitted on Feb. 28, 1938, with obstructive jaundice. The serum bilirubin was 10.5 and the serum lipase 5.0. The fasting blood sugar was 74 on admission but three days later the blood sugar was 208. The diagnosis of diabetes mellitus seemed established and the patient was placed on insulin therapy. On March 14, 1938, a cholecystojejunostomy was performed. At operation, the surgeon noted an irregular enlargement of the head of the pancreas. No biopsy was taken. The serum bilirubin concentration progressively decreased after the operation and on April 5, 1938, it was 0.4 milligrams. At the time of discharge on April 8, 1938, the patient was advised to continue with insulin therapy. On May 17, 1938, he was re-admitted to the hospital with almost complete obstruction at the junction of the first and second portions of the duodenum. A posterior gastrojejunostomy was performed on May 25, 1938. The head of the pancreas was larger, the duodenal obstruction was thought to be the result of extension of the pancreatic malignancy. Two small metastatic nodules were seen in the liver. No biopsy

was taken. The patient died on July 17, 1938, from a cerebral hemorrhage. An autopsy was not permitted.

COMMENT

Ten serum lipase determinations were carried out in this instance, the first being reported on March 1, 1938, at the time of the second hospital admission. As the pancreatic malignancy progressed the severity of the diabetes coincided with the progressive decrease in serum lipase values over a period of approximately three months. On May 19, 1938, about two months before death the serum lipase value was within the normal range. We believe that the initial rise in the serum lipase value coincided with obstruction probably, of the main pancreatic duct. It is probable that as the disease progressed either pancreatic exhaustion or replacement of actively functioning pancreatic tissue occurred. Particularly noteworthy in that respect was the gradually progressive diminution in the serum lipase values. An isolated normal serum lipase value on May 19, 1938, two months before death, would have been misleading in that there would have been no hint of the actual progression of events as portrayed in the whole series of serum lipase determinations. The following pertinent laboratory data were recorded:

Date	Serum Lipase	Serum Bilirubin	Bromsulphthalein Per Cent Retention
First admission 12-30-37 to 1-24-38			
3-1-38	5.0	10.5	
3-6-38	9		
3-14-38	Cholecysto-jejunostomy		
3-15-38		6.0	
3-16-38		6.5	
3-17-38		8.0	
3-19-38	4.2	7.5	
3-22-38	4.2	4.0	
3-26-38	3.5	3.0	
3-29-38	3.5	1.2	
3-31-38		1.7	
4-2-38		1.2	0
4-6-38	2.9		
Out Patient			
4-10-38	2.1		
4-12-38	1.9	0.8	0
Third admission 5-17-38 to 7-17-38			
6-18-38	0.48	1.2	
5-25-38	Gastro-jejunostomy		

Case W. B., a male negro, 59 years of age, was seen first in the out-patient department on October 17, 1940, with a history of daily upper abdominal pain for 6 weeks. Ingestion of food increased the pain. There had been progressive weakness and loss of weight. Physical examination disclosed an irregular mass in the upper abdomen. There was slight icterus of the sclerae. The patient was admitted to the Graduate Hospital on October 28, 1940. On November 18, 1940, Dr. W. E. Lee performed a cholecystojejunostomy. At operation the pancreas was enlarged, the liver studded with metastatic nodules. A biopsy of one of the liver nodules showed adenocarcinoma on microscopic section. The patient reacted satisfactorily in the post-operative period but became progressively weaker and expired on December 11, 1940. A severe diabetic condition intervened which was controlled with

insulin. The following pertinent laboratory data were recorded:

Date	Serum Lipase	Serum Bilirubin	Bromsulphthalein Per Cent Retention
10-22-40	2.12	3.2	65
10-25-40	2.60		
10-29-40		6.0	
11-2-40	1.60	9.0	
11-5-40		7.0	85
11-13-40	0.32		
11-14-40			
Operation			
11-21-40		3.0	
12-2-40		1.5	
12-9-40	0.24	1.5	

COMMENT

This hyposensitive patient was in a cachectic state before he presented himself for treatment. The serum lipase activity already had dropped to within the normal range (0.32) approximately one week prior to operation. It is evident that of 5 serum lipase determinations in this case the last 2 determinations in themselves would afford no diagnostic aid to indicate the presence of advanced pancreatic malignancy.

Case A. L., a white female, 54 years of age, was admitted to the Graduate Hospital on January 14, 1940, with severe nasal bleeding of two days duration during which her family estimated that she had lost 3 pints of blood. There was a history of recent progressive weakness and loss of weight. Jaundice first was noted two weeks prior to admission. She did not complain of abdominal pain but anorexia was present. Physical examination revealed a globular mass in the region of the gall bladder. The initial reading of the prothrombin time (Quick) was 51 seconds (78 per cent). The nasal bleeding was controlled by a nasal pack and the administration of Vitamin K. On January 27, 1940, Dr. W. E. Lee performed a cholecystogastrostomy and gastrojejunostomy. At operation the mass in the upper right quadrant was a distended gall bladder. Dr. Lee was able to palpate a mass two inches in diameter at the head of the pancreas. No biopsy was taken. Post-operatively, although the jaundice improved the patient experienced a progressively downward course and expired on May 31, 1940. The following pertinent laboratory data were recorded:

Date	Serum Lipase	Serum Bilirubin
1-15-40		10.0
1-24-40		16.0
1-27-40		
Operation	0.28	
2-1-40		7.0
2-7-40		3.0
3-2-40		0.9
3-19-40	2.70	1.4
3-29-40	4.20	
4-6-40	3.20	
5-3-40	0.12	
5-14-40	0.14	

COMMENT

Six serum lipase determinations were recorded. The first and last two determinations were within normal limits. The behavior of the serum lipase curve in this case is perhaps unusual. The concentration of the enzyme in the serum did not increase during the phase of complete obstructive jaundice. Perhaps the obstruction to the pancreatic duct was not complete at

this time. The enzyme exhaustion of extensive disease could not have accounted for the absence of hyperlipasemia since a pathological elevation in the lipase value in the serum occurred two months later. At that time the serum bilirubin concentration had become almost normal because of the short-circuiting operation. This may correspond to the occurrence of complete obstruction to the pancreatic duct. About one month before death two estimations revealed an almost complete absence of the lipolytic enzyme in the serum, i. e., the stage of pancreatic exhaustion or almost complete destruction of pancreatic tissue.

TECHNICAL ASPECTS OF THE SERUM LIPASE DETERMINATIONS

Certain technical aspects of the serum lipase determination require comment. One of the most valid criticisms of the test concerns the variability of the substrate. Olive oil is not a stable organic substance and there is reason to believe that various lots of olive oil might vary in the ease with which they break down into glycerin and fatty acid. In our first reported series we used the 50 per cent olive oil substrate prepared by the Abbott Laboratories in accordance with the specifications of Cherry and Crandall (6). We noticed that at the completion of the 24 hour test period the suspension of olive oil substrate and serum remained uniform, thus suggesting that the serum and substrate remained in close contact during the whole test period and assuring the maximum effect of the serum lipase on the olive oil. About March, 1940 (8) a new lot of substrate was prepared by the Abbott Laboratories, labeled "Olive Oil Emulsion. Use as a reagent in the determination of the lipase in blood serum according to the method of Comfort and Osterberg." We noted immediately that at the completion of the 24 hour test period, instead of the uniform suspension noted with the previous preparation of substrate, a separation occurred with the new substrate in such a manner that at the end of the 24 hour test period the full amount of substrate in the test (20 cc) appeared in a layer at the top of the test tube, indicating that the serum and substrate had not remained in close contact for the duration of the 24 hour test period. That phenomena suggested that the new substrate might not be as effective as the previous substrate in detecting elevations in the serum lipase. Fewer elevated serum lipase values were noted in cases similar to those in which elevated values were obtained previously. Inquiry (8) of the Abbott Laboratories developed that the newer substrate had been prepared with the use of a different type of homogenizer thus altering the physical but presumably not the chemical properties of the substrate. It was suggested that the suspension of serum and substrate in the test be shaken every few hours to insure more intimate contact between the serum and substrate, a practical impossibility using a 24 hour test in a routine laboratory. An experimental batch of identical substrate was prepared for us by Dr. Tabern of the Abbott Laboratories to which had been added one-half per cent Tergitol-7 with the purpose of promoting a more uniform suspension. The Tergitol-7 preparation gave normal values when run in parallel with the regular olive oil substrate using normal sera. However, in cases with expected elevated serum lipase values the Tergitol-7 preparation gave values twice that of the regular olive oil substrate, and more like

those obtained with the original olive oil substrate of Cherry and Crandall. We suggest that the Tergitol-7 preparation is the more sensitive one and should be used in preference to the present olive oil substrate. It is obvious that such variations in the physical properties of the olive oil emulsion make for some confusion in the interpretation of serum lipase reports from different institutions.

SUMMARY

1. Selected data were presented from a series of 1200 serum lipase determinations on 800 patients.

2. The behavior of serial serum lipase determinations was analyzed in a selected group of 5 cases of acute pancreatitis, one case of chronic pancreatitis and 3 cases of malignancy of the pancreas.

3. Analysis of our cases of acute pancreatitis suggests that the decrease in serum lipase concentration following an initial elevated serum lipase may be due either to a subsiding of the inflammatory process or to complete destruction of the pancreas. There were 21 cases of acute pancreatitis, in 17 of which (81%) the serum lipase was elevated.

4. The serum lipase curve in one case of chronic pancreatitis was indistinguishable from that of pancreatic malignancy.

5. The serum lipase curves in cases of pancreatic malignancy suggest that the initial elevation of the concentration of serum lipase is due to an obstruction to the free flow of pancreatic juice. The subsequent decrease in the concentration of the serum lipase is due either to replacement of pancreatic tissue by the malignant process or to impaired pancreatic function secondary to prolonged pancreatic duct obstruction. There were 30 cases of malignancy of the pancreas in 16 of which (53.3%) the serum lipase was elevated.

6. Certain limitations of the serum lipase determination are discussed with reference to the variability of the olive oil substrate.

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DISCUSSION

DR ERNEST H. GAITHER (Baltimore), Mr. President and Members of the Association: I am sure that everyone is always keenly interested in any and all work wherein the pancreas is concerned, for to date it has certainly proved most elusive from the standpoint of early and correct diagnosis.

The difficulties which beset us all in days gone by when endeavoring to obtain worthwhile evidence of pancreatic disease by studying the enzymes is fully appreciated by all investigators. Therefore we hail with keen interest and delight any measures which bid fair to be of diagnostic value in this domain.

Progress is being made and I think that a little later we are going to find some tests which will produce early

and valuable information for after all, that is what we most desire.

I should be remiss in concluding if I did not congratulate the authors on this perfectly splendid and helpful piece of work, and I am sure that it augurs well for the future in establishing an early diagnosis in disease of the pancreas

DR MANDRED W COMFORT Rochester, Minn) Determination of the lipolytic activity of serum is of value in the diagnosis of benign and malignant diseases of the pancreas It is of interest to recall that one of the members of this Society, Crandall, collaborated with Cherry on the fundamental work on which is based the method by which determination of the lipolytic activity in the serum is carried out

Determination of the activity of amylase in the serum is likewise of value in the diagnosis of pancreatic disease and both tests are now available for routine use at the Mayo Clinic.

I believe, however, that the determination of the value for lipase in the serum possesses two advantages over the determination of the value for amylase Values for lipase in the serum may remain elevated for longer periods of time than do values for amylase. At the Clinic, we do not always see patients within the first few hours or days of

the disease, this may be of great significance Second, in our experience, values for lipase in the serum are elevated in a greater percentage of cases of carcinoma of the pancreas than are values for amylase The determination of values for amylase has the advantage of requiring a much shorter time for its performance Actually, there is an advantage in doing both tests because sometimes the value for one enzyme is elevated while that for the other is not.

Determinations of values for enzymes in the serum are especially useful in the diagnosis of acute pancreatitis of chronic pancreatitis with recurring exacerbations, and of malignant lesions of the pancreas but the results should be used in conjunction with all available clinical data

DR THOMAS A JOHNSON (Philadelphia) There is very little for me to add We have done none of the original work with this test All we did was apply the test to our material

I was interested in Dr Comfort's remarks concerning amylase Unfortunately, we have been unable to do the serum amylase I have a feeling that perhaps in the acute case there is more value in the serum amylase because the serum amylase can be determined within a short time, half an hour or an hour, whereas one has to wait twenty-four hours for the lipase

External Pancreatic Fistula Report of a Case With Physiologic Observations*

By

MANDRED W COMFORT, M.D.,† ARNOLD E OSTERBERG, Ph.D.‡

and

JAMES T PRIESTLEY, M.D.§
ROCHESTER MINNESOTA

SEVERAL patients who had an external pancreatic fistula have been seen at the Mayo Clinic during the past few years Attempts to study the secretion of pancreatic juice among these patients in the main have been unsatisfactory for one reason or another, the patient was too ill for study or drainage of the secretion from the fistulous tract would have been unsatisfactory without placing the patient in positions at the time impossible, or the secretion contained so much mucopurulent material that the results of quantitative analysis would have been unreliable Recently, however, we had the opportunity to study a case in which none of the objections were found The patient was a healthy, active man, the fistulous tract had been kept open with a rubber catheter so long that the tract was epithelialized, and the secretion was clear and uninfected We were fortunate in being able to proceed with certain physiologic observations on the patient for a short period Circumstances forced us to discontinue our observations earlier than we had planned, but the data seem extensive and interesting enough to record The case itself is worthy of reporting so that there may be added to the few previously reported cases another case of external pancreatic fistula successfully treated surgically

REPORT OF A CASE

A man thirty-nine years old registered at the clinic on November 8, 1940 The family history was irrelevant. Four years prior to the patient's admission three or four attacks of severe upper abdominal pain had occurred Each had lasted thirty to sixty minutes and required the hypodermic injection of morphine sulfate for relief As much as 1 grain (0.065 gm) of morphine sulfate had been required for relief during one attack Three years prior to the patient's admission a very severe attack of pain associated with abdominal distention had occurred Surgical exploration had revealed a pancreatic cyst from which 1½ gallons (approximately 6 liters) of fluid had been removed, a drain had been inserted and the fistula had persisted since that time This drained about ½ pint (237 cc) of liquid each day through a catheter which was kept in place in the fistulous tract Attempts had been made to close the fistula by dietary measures and sclerosing solutions, without effect On November 6, 1940, he had experienced a severe attack of epigastric pain which extended through to the back, associated with severe chills which endured for three hours and pain which lasted twenty-four hours Dark brown urine was passed on the next morning

On November 11, three days after the patient's registration at the clinic, another attack of severe pain in the right upper abdominal quadrant had occurred The pain extended through to the back, lasted from 3 00 to 5 00 o'clock in the morning, and was associated with vomiting

Results of a general physical examination were essentially negative, with the exception of a large fistulous tract situated just above the umbilicus In this tract a

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†Division of Medicine.

‡Division of Biochemistry

§Division of Surgery Mayo Clinic, Rochester Minn

No 28 French soft rubber catheter was taped into position and connected to a bottle. There was tenderness of some degree in the right upper quadrant of the abdomen.

Results of urinalysis were negative, the value for hemoglobin was 13.8 gm per 100 cc., erythrocytes numbered 4,650,000 and leukocytes 6,300 per cubic millimeter. Result of the routine serologic test for syphilis was negative, and roentgenograms of the thorax, kidneys, ureters and bladder disclosed nothing abnormal. Special roentgenograms of the pancreatic region showed the drainage tube to be in position. Cholecystograms revealed a nonfunctioning gall bladder. The concentration of blood urea was 22 mg per 100 cc. Urea clearance was normal.

The diagnosis was "chronic cholecystitis with stones and external pancreatic fistula." Operation was performed on December 5, 1940. Very little inflammatory reaction was seen around the fistulous tract, which was of large caliber because of the effects of the No 28 French catheter which

was present throughout the entire pancreas, but especially in the region of the head and body of the gland. The gall bladder was found to contain stones and accordingly, cholecystectomy was performed. The liver was in good condition. The wound was closed and drainage was instituted.

The patient's immediate post-operative course was without event. Since he was rather obese and since the incision was a secondary one, he was kept in bed for two weeks and then dismissed from the hospital on the eighteenth post operative day. When we last heard from him in May, 1941, the patient apparently was well and had no complaints to offer.

PHYSIOLOGIC OBSERVATIONS

Technic of collecting fractions of pancreatic juice
—Pancreatic juice secreted through the tube in the ex-

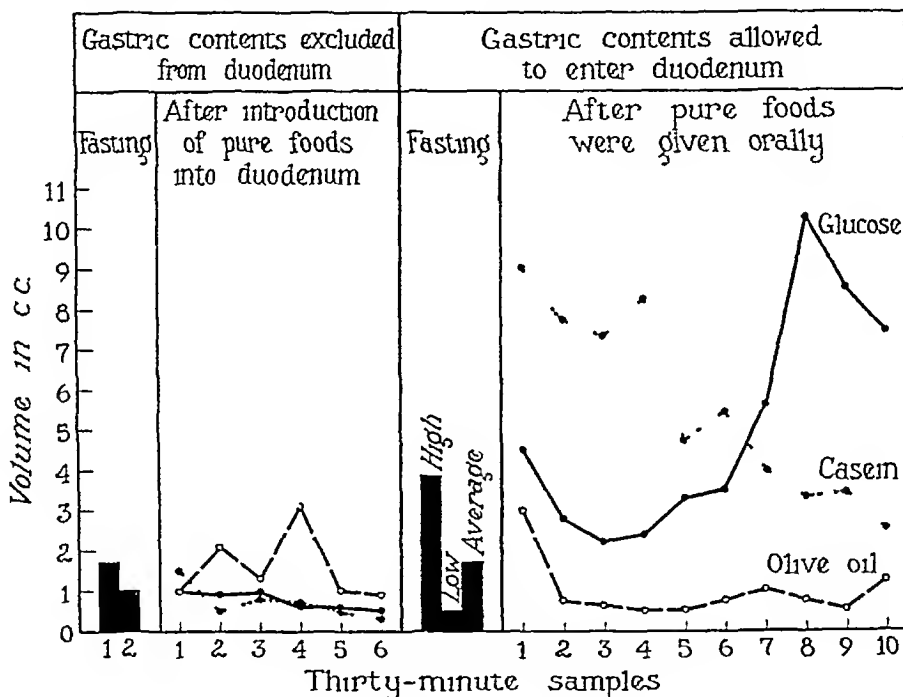


Fig 1 The effect of glucose, casein and olive oil introduced by tube directly into the duodenal cavity (gastric contents excluded from duodenal cavity) contrasted with the effect of glucose, casein and olive oil administered orally (gastric contents allowed to enter duodenum) on the volume of pancreatic secretion from an external pancreatic fistula

had been maintained in position. The fistulous tract appeared to be well epithelialized, probably because of the length of time it had been present. An old scar resulting from a left rectus incision was excised, and the fistulous tract was preserved. The fistula arose from approximately the midportion of the pancreas and proceeded through the gastroduodenal omentum just below the greater curvature of the stomach. It was possible to transplant the fistulous tract into the anterior wall of the stomach near the greater curvature without undue angulation or constriction of the fistula. Accordingly, this was done. Two leading or guide sutures of fine chromic catgut were utilized to lead the fistulous tract into the lumen of the stomach for a distance of approximately 1.5 cm. The fistula was then maintained in position with a row of interrupted catgut sutures and two rows of interrupted silk sutures which brought the anterior gastric wall up around the fistulous tract. The operative region was then protected with nearby omentum. Considerable induration

external pancreatic fistula was collected in thirty-minute samples. The juice was collected in graduated centrifuge tubes to facilitate measurement of volume in cubic centimeters.

Chemical methods—The hydrogen ion concentration (pH) was determined by the quinhydrone electrode method. The bicarbonate content was determined by the amount of carbon dioxide liberated in the volumetric apparatus of Van Slyke. Amylase activity was determined by the method of Norby, as modified by Agren and Lagerlof (1). The activity of lipase was determined by the method of Crandall and Cherry (2), as reported by Parker and two of us (Comfort and Osterberg (3)) in previous studies. We used a 1 to 10 dilution of specimens obtained from the fistula.

Secretion of the pancreas through the external pancreatic fistula when gastric juice is excluded from

TABLE I
Volume of pancreatic juice

Specimen No	Stimulant Type	Observations																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
		Chemical	Carbo- hydrate, gm	Protein gm	Fat gm	Pancreatic juice cc												
		20			100			114	110	113	112	42	63	59				
			10			25		33	27	32	7	51	15	14				
				30			0	15	13	16	17	41	37	37				
1		1.0	1.5	1.0	4.5	9.0	3.0	2.5	2.0	4.4	6.5	4.0	9.8	8.3	3.0	5.1	0.7	4.1
2		0.9	0.5	2.1	2.8	7.7	0.75	4.9	7.5	2.5	6.1	3.1	4.4	3.9	3.2	4.6	0.5	4.0
3		1.0	0.9	1.3	2.2	7.3	0.65	5.3	7.0	1.5	8.3	4.6	5.1	2.5	2.2	4.9	0.5	4.0
4		0.6	0.7	3.1	2.4	8.2	0.50	5.0	7.2	2.5	6.4	4.5	7.5	2.0	4.5		0.3	2.6
5		0.6	0.5	1.0	3.3	4.7	0.50	4.3	11.0	2.0	3.7	3.4	4.0	1.6	2.0		0.3	3.4
6		0.5	0.3	0.9	3.5	3.4	0.75	4.5	9.0	1.4	5.4	3.9	4.6	1.5			0.9	2.5
Total		4.6	4.3	9.4	18.7	42.3	6.15	26.5	44.6	14.3	36.4	23.5	35.4	19.8	14.9		3.2	20.5
7				0.6	5.6	4.0	1.0	8.5	6.4	2.0	6.2	3.8						
8				0.6	10.2	3.3	0.75	8.0	5.5	3.6	7.5	3.2						
9				2.3	8.5	3.4	0.5	8.0	7.8	4.4	3.0	3.0						
10				7.4	2.5	1.25	4.9	5.3	3.5	3.0								
Total				50.5	55.5	9.65	55.9	65.6	27.8	56.1	33.5							

- 1 E—Ephedrine sulfate 3.4 grain (H) at start of collection of first specimen
 2 A—Atropine sulfate 1.75 grain (H) at start of collection of first third and fifth specimen
 3 S—Secretin 1 clinical unit per kilogram of body weight intravenously
 4 M—Acetyl beta methylcholine chloride 15 mg (H)
 5 S and M—Combined stimulation by secretin and acetyl beta methylcholine chloride
 6 Experiments 1 to 3—Foods given directly into duodenum from which gastric juice was excluded.
 7 Experiments 4 to 13—Foods given orally
 8 Experiments 1 to 13—All specimens collected over thirty minute periods
 9 Experiments 14 to 17—Specimens 1, 2, 3 and 4 collected over ten minute periods specimens 5 and 6 collected over twenty minute periods

the duodenum Technic—A double-barreled gastro-duodenal tube was introduced into the stomach and duodenum. Confirmation of the fact that the tube occupied the correct position was made roentgenologically. Continuous aspiration through the gastric barrel of the tube was maintained under negative pressure of 25 inches (63.5 cm) of water, to prevent the entrance of acid gastric juice into the duodenum and to eliminate the influence of gastric contents on the secretin mechanism.

Fasting secretion—The fasting secretion of the pancreas through the external pancreatic fistula, with gastric juice excluded from the duodenum by the aforementioned technic, was studied during two thirty-

minute periods. During these periods the volumes were, respectively, 17 and 10 cc. The concentration of bicarbonate in millimols per cubic centimeter was, respectively, 0.06 and 0.07. The total bicarbonate in millimols per specimen was 0.10 and 0.07. The concentration of amylase was, respectively, 2.4 and 1.0 mg of maltose for each cubic centimeter of pancreatic juice, values for amylase per specimen were, respectively, 4.4 and 1.0 mg of maltose. The concentration of lipase was, respectively, 222 and 226 cc of twentieth-normal sodium hydroxide for each cubic centimeter of pancreatic juice, the values for total lipase per specimen were, respectively, 377 and 226 cc of twentieth-normal sodium hydroxide.

TABLE II
Values for pH

Specimen No	Stimulant Type	Observations																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
		Chemical	Carbo- hydrate, gm	Protein gm	Fat gm	Hydrogen ion concentration												
		20			100			114	110	113	112	42	63	59				
			10			25		33	27	32	7	51	15	14				
				30			60	15	13	16	13	41	37	37				
1			8.21		8.04	8.17				8.04	8.12		8.12	7.84	7.90	8.0		7.53
2			7.95		8.38	8.21		8.17	8.35			7.36		8.24	8.16	8.25		7.53
3			7.87		8.38	8.38				8.28	8.12			8.17	8.38	8.25		8.20
4			7.8		8.24	8.29						8.12	8.12	8.17	8.38			8.29
5					8.24	8.21				8.14				7.90	8.38			8.29
6					8.24	8.06								7.90				8.29
7					8.21	8.12		8.04		8.04				7.90				
8					8.21	8.21						8.12						
9					8.21	8.04			8.21	8.21								
10					8.21	7.90					8.24							

- 1 E—Ephedrine sulfate 3.4 grain (H) at start of collection of first specimen
 2 A—Atropine sulfate 1.75 grain (H) at start of collection of first third and fifth specimen
 3 S—Secretin 1 clinical unit per kilogram of body weight intravenously
 4 M—Acetyl beta methylcholine chloride 15 mg (H)
 5 S and M—Combined stimulation by secretin and acetyl beta methylcholine chloride
 6 Experiments 1 to 3—Foods given directly into duodenum from which gastric juice was excluded
 7 Experiments 4 to 13—Foods given orally
 8 Experiments 1 to 13—All specimens collected over thirty minute periods
 9 Experiments 14 to 17—Specimens 1, 2, 3 and 4 collected over ten minute periods specimens 5 and 6 collected over twenty minute periods

Secretion after the introduction of pure foods directly into the duodenum—Twenty grams of glucose in 200 cc of water, 10 gm of casein in 60 cc of water to which a few drops of ammonium hydroxide were added, and 60 cc of a 50 per cent emulsion of olive oil in water were introduced through the duodenal barrel of the gastro-duodenal tube, respectively, in observations 1, 2 and 3

The volume of pancreatic juice in cubic centimeters secreted during the thirty-minute periods after the introduction into the duodenum of glucose and casein (observations 1 and 2, Table I) remained small, and with the exception of the first thirty-minute sample, less than the lesser of the two volumes obtained with fasting conditions (Fig 1) The volume of pancreatic

casein. The differences were marked, however, only in the second and fourth periods. In summary, the values for fluid volume after the introduction of glucose and casein did not rise above values seen under fasting conditions. Actually, the fluid volume of pancreatic juice progressively declined after the introduction of glucose and casein. On the contrary, the values for fluid volume after the introduction of olive oil did not decline, but only those for the second and fourth period after the introduction of olive oil increased above the values seen under fasting conditions

The values for pH after the introduction of casein into the duodenum were decreased from 8.21 to 7.78 (Table II). The values for concentration of bicarbonate in millimols per cubic centimeter of pancreatic

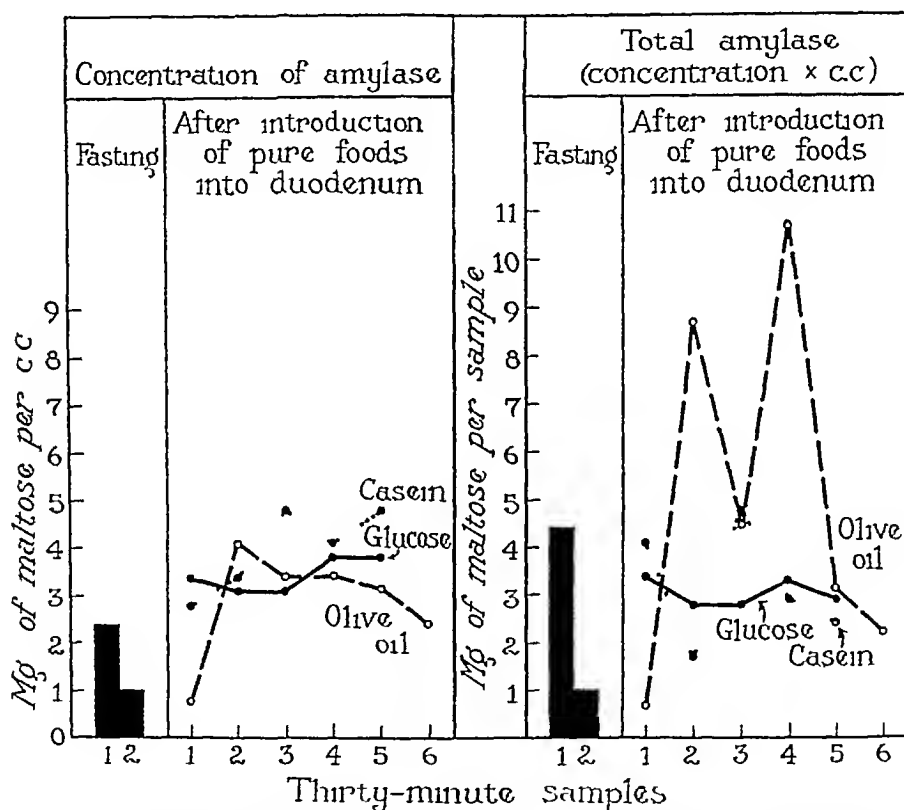


Fig. 2 The effect of glucose, casein and olive oil introduced directly into the duodenal cavity on the concentration and total secretion of amylase in the pancreatic juice, secreted through an external pancreatic fistula, while the gastric contents were excluded from the duodenum

juice secreted after the introduction of olive oil into the duodenum (observation 3, Table I) likewise remained small (Fig 1). The volumes of pancreatic juice collected during the first, fifth and sixth thirty-minute periods after the introduction of olive oil were equal to the lesser of the two volumes obtained under fasting conditions, the volumes of pancreatic juice which were collected during the second and fourth thirty-minute periods alone exceeded the larger of the two volumes of fasting pancreatic juice. It may be significant that the volume of pancreatic juice for each thirty-minute period after the introduction of olive oil, with the exception of the first period was greater than the volume obtained during corresponding periods after the introduction of glucose and

juice and for the total bicarbonate per sample of pancreatic juice after the introduction of glucose into the duodenum were low in the samples analyzed (observation 1, Table III) and were less than the values obtained under fasting conditions (concentration 0.06 to 0.07, total per sample 0.10 and 0.07). The concentrations of bicarbonate in millimols per cubic centimeter of pancreatic juice in the first three samples after the introduction of olive oil (observation 3 Table III) into the duodenum were less than those obtained under fasting conditions, but those in samples 4, 5 and 6 progressively increased, reaching values equal to those obtained under fasting conditions. The values for total bicarbonate per sample of pancreatic juice after the introduction of glucose and olive oil

(observations 1 and 3, Table III) definitely increased above the values obtained under fasting conditions only in the fourth sample after the introduction of olive oil

The concentrations of amylase in the samples of pancreatic juice obtained after the introduction of glucose, casein and olive oil (observations 1, 2 and 3 Table IV Fig 2) into the duodenum were greater on the whole than the concentrations of amylase in the samples of pancreatic juice obtained under fasting conditions (2.4 and 1.0 mg maltose per cubic centimeter of pancreatic juice)

The concentrations of amylase exhibited a tendency to be higher after the introduction of glucose and casein into the duodenum than after the introduction of olive oil. The values for total amylase in the samples obtained during all the thirty-minute periods after the introduction of glucose, casein and olive oil (observations 1, 2 and 3 Table IV, Fig 2) were well within the range encountered in samples obtained under fasting conditions (4.4 and 1.0 mg of maltose) with the exception of those in the second and fourth thirty-minute samples after the introduction of olive oil. These latter values were well above those found in samples obtained under fasting conditions.

The concentration of lipase in the samples of pancreatic juice obtained after the introduction of glucose, casein and olive oil (observations 1, 2 and 3 Table V, Fig 3) into the duodenum were approximately equal to or less than the concentration of lipase

in the samples obtained under fasting conditions (222 and 226 cc of twentieth-normal sodium hydroxide per cubic centimeter)

The values for total lipase per sample of pancreatic juice after the introduction of glucose, casein and olive oil were less (Fig 3) than the highest value obtained in a sample under fasting conditions (377 cc of twentieth-normal sodium hydroxide), except for those obtained in samples 2 and 4 after the introduction of olive oil, which were greater than those obtained in samples under fasting conditions. The values for concentration and for total lipase after olive oil were slightly greater than those after glucose and casein.

Comment—The values for fluid volume, total bicarbonate, total amylase and total lipase per unit of time did not increase to more than fasting values after the introduction of glucose and casein into the duodenum. Actually, these values remained essentially unchanged or gradually declined after the introduction of these foods into the duodenum. Although the values for fluid volume, total bicarbonate, total amylase and lipase increased to more than fasting values, only in the second and fourth samples obtained after the introduction of olive oil (observation 3, Tables I, III, IV and V) into the duodenum, the values for fluid volume, total bicarbonate, total amylase and total lipase per sample, were, on the average, higher after the introduction of olive oil than in fasting samples and the total values for fluid volume, amylase and

TABLE III
Concentration of bicarbonate in millimols per cc

Specimen No	Stimulant Type	Observations															
	Chemical	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Carbohydrate, gm.	20			100			114	110	113	112	42	63	59			
	Protein, gm.		10			25		33	27	32	7	51	16	14			
	Fat, gm.			30			60	15	13	16	13	41	37	37			
		Bicarbonate millimols per cc															
1		0.04		0.05	0.07	0.07	0.07		0.05	0.05	0.07			0.09	0.08	0.09	0.05
2		0.05		0.05	0.08	0.11		0.08	0.08	0.05	0.07			0.10	0.11	0.10	0.05
3				0.05	0.08	0.12	0.07	0.09		0.06		0.07		0.08	0.11	0.09	0.05
4				0.06	0.07	0.11	0.03	0.07			0.10	0.07		0.07	0.10		0.10
5				0.07	0.07	0.09	0.05	0.10		0.06	0.07	0.05		0.06	0.10		0.10
6				0.07	0.08	0.09		0.09		0.06	0.09	0.04		0.06			0.09
7				0.08	0.07	0.08	0.03	0.05	0.09	0.08	0.09	0.07					
8					0.10	0.08		0.07			0.09	0.07					
9					0.10	0.05	0.03	0.07			0.09	0.07					
10					0.10	0.05	0.04	0.07			0.08						

Total bicarbonate per specimen (concentration times cc)

1	0.01	0.06	0.32	0.81	0.21		0.35	0.13	0.28		0.75	0.24	0.46	0.09	0.21
2	0.05	0.11	0.22	0.85	0.39	0.06	0.15	0.31	0.21		0.39	0.36	0.46	0.09	0.51
3		0.07	0.18	0.88	0.05	0.45		0.09	0.37		0.20	0.24	0.46	0.09	0.40
4		0.18	0.17	0.90	0.04	0.35			0.64	0.36	0.14	0.46			0.25
5		0.07	0.23	0.42	0.05	0.43		0.12	0.33	0.27	0.10	0.20			0.34
6		0.07	0.24	0.43	0.07	0.41		0.18	0.19	0.31	0.12				0.23
Total		0.56	1.40	4.29	0.42	2.06	0.89	2.10	1.75		1.70	1.40			1.94
7		0.05	0.50	0.36	0.08	0.68	0.08	0.16	0.56	0.27					
8			0.10	1.02	0.26	0.05	0.56		0.65	0.22					
9			0.12	0.85	0.27	0.04	0.56		0.27	0.21					
10				0.74	0.20	0.09	0.34		0.24						
Total			0.83	4.50	5.38	0.88	4.17		3.85	2.45					

1 E—Ephedrine sulfate 3.4 grain (H) at start of collection of first specimen

2 A—Atropine sulfate 1/75 grain (H) at start of collection of first third and fifth specimen

3 S—Secretin 1 clinical unit per kilogram of body weight, intravenously

4 M—Acetyl beta methylcholine chloride, 15 mg (H)

5 S and M—Combined stimulation by secretin and acetyl beta methylcholine chloride

6 Experiments 1 to 3—Foods given directly into duodenum from which gastric juice was excluded

7 Experiments 4 to 13—Foods given orally

8 Experiments 1 to 13—All specimens collected over thirty-minute periods

9 Experiments 14 to 17—Specimens 1, 2, 3 and 4 collected over ten minute periods; specimens 5 and 6 collected over twenty minute periods

lipase (observations 1, 2 and 3, Tables I, IV and V) were greater after the introduction of olive oil than after the introduction of glucose and casein into the duodenum

In short, glucose and casein in the amounts used, in water, when introduced directly into the duodenum, from which the gastric contents were excluded, did not stimulate pancreatic secretion. On the contrary, olive oil stimulated pancreatic secretion, especially during the second and fourth thirty-minute periods after introduction into the duodenum. Food when introduced directly into the duodenum, from which the gastric juice had been excluded by continuous suction, produced similar effects on pancreatic secretion aspirated from the duodenum, carbohydrates and proteins did not, while fats did, increase the output of fluid volume, bicarbonate and enzymes during stimulation with secretin administered intravenously (4). Similarly, in the experimental laboratory, glucose

been described (5). The "quick" action does not occur regularly in the experimental animal (6) and was not recognized in observation 3 on our subject. The increased flow of pancreatic juice that followed administration of olive oil, which flow was slightly greater than that which followed the administration of glucose and casein in our case (Fig 1), may well be the delayed or secondary stimulation by fat observed in the experimental animal. The amount of pancreatic secretion in the second and fourth stimulation periods, however, was out of proportion to that of the other thirty-minute periods (Figs 1-3). The uneven character of secretory response suggests that some other factor acting intermittently produces the added secretion in the second and fourth thirty-minute periods. Intermittent evacuation of gastric contents into the duodenum produces such an effect on pancreatic secretion. Intermittent spilling over of the gastric contents into the duodenum may have occurred

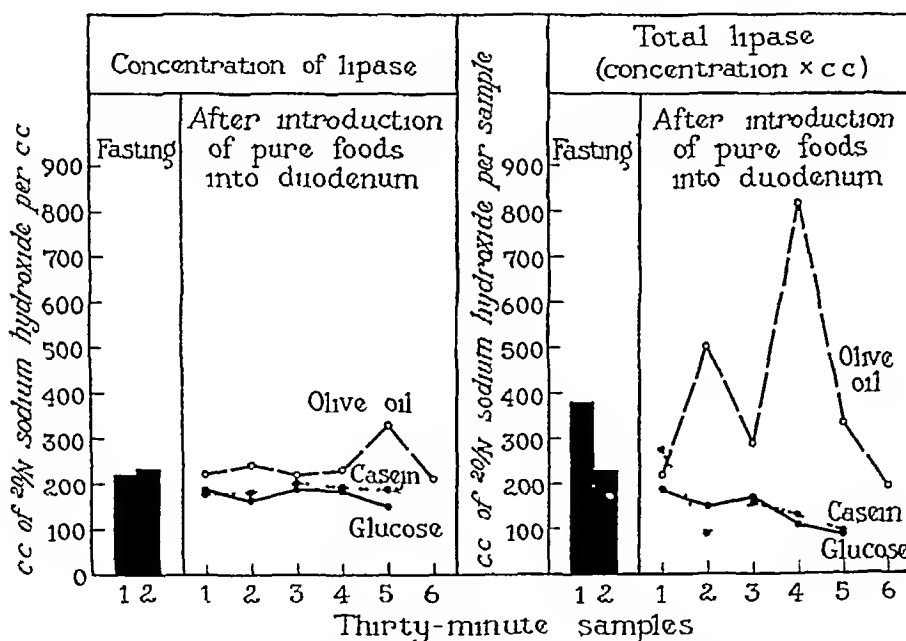


Fig 3 The effect of glucose, casein and olive oil introduced directly into the duodenal cavity by tube on the concentration and total secretion of lipase per unit of time in the pancreatic juice secreted through an external pancreatic fistula, while the gastric contents were excluded from the duodenum

and casein apparently do not stimulate directly pancreatic secretion, while olive oil does do so, as was the case in these observations on our subject. After reviewing the literature, Ivy (5) wrote "It appears that carbohydrate excites pancreatic secretion only through the appetite secretion of gastric or pancreatic juice they call forth," and "It appears from this evidence that the proteins excite pancreatic secretion primarily. If not entirely through their effect on the gastric glands, or the excitation of the pancreas by proteins is due to the gastric secretion they excite acting in the intestine."

Since the effect of gastric secretion has presumably been eliminated in observations 1 and 2 the absence of stimulation of the pancreas after the administration of glucose and casein was not unexpected. In the experimental laboratory both a quick and a delayed stimulation of pancreatic secretion by fat have

during the second and fourth periods, in spite of continuous suction, and may have been a factor in causing the greater increase in volume, total amylase and total lipase seen in the second and fourth periods after the introduction of olive oil over volume, total amylase and total lipase noted in the other periods (Figs 1-3).

Water alone stimulated secretion in the experimental animal directly by way of the intestine, and its maximal effect (300 to 500 cc) is reached in about one hour (5). If the small amounts of water, in which the glucose and casein were administered in these observations stimulated pancreatic secretion, such an effect was not observed.

The concentrations of amylase increased to more than fasting levels. Those of lipase were essentially unchanged after the introduction of glucose, casein and olive oil into the duodenum. The fact that the concentration of amylase in the pancreatic juice after

the introduction of glucose, casein and olive oil into the duodenum was greater than the concentration of amylase under fasting conditions suggests that foods stimulate the secretion of amylase in greater concentrations than are seen under fasting conditions. Since it is known however that the concentration of amylase varies inversely according to the rate of secretion under some conditions, it is possible that the high concentrations of amylase noted in these observations were the effects of concentration brought about by the very small volumes of pancreatic juice secreted. Concentrations of lipase as determined by the method of Cherry and Ciandall have not clearly varied with the rate of secretion in these observations, or in those previously reported by two of us (7).

Secretion of the pancreas through the external pancreatic fistula without exclusion of gastric juice from the duodenum. Fasting secretion—The collection of thirty-minute fractions was started at 3 00 o'clock in the morning nine hours after the subject's last meal and was continued until 8 00 o'clock in the morning. The volume for the successive thirty-minute periods was 0.5, 2.0, 3.0, 1.0, 1.0, 0.9, 0.4, 3.9, 2.5 and 2.0 cc. The average volume per thirty-minute period was 1.7 cc. The concentration of bicarbonate in millimols for the successive thirty-minute periods was respectively 0.08, 0.07, 0.08, 0.08, 0.07, 0.08, one not determined, 0.07, 0.09 and 0.08, for each cubic centimeter of pancreatic juice. The value for total bicarbonate in millimols per specimen was respectively,

0.04, 0.14, 0.24, 0.08, 0.07, 0.07, one not determined, 0.33, 0.23 and 0.16.

Comment—The volume and secretion of bicarbonate during the fasting state was low. The patient slept well until 6 30 in the morning. The increase in secretion between 3 30 and 4 30 in the morning suggests a periodic secretory activity of the stomach and pancreas. The patient awakened at 6 30, arose and shaved. The secretion increased with activity and with the approach of meal time.

Secretion after the oral administration of pure foods—In observations 4, 5 and 6, respectively, 100 gm of glucose in 300 cc of water, 25 gm. of casein in 100 cc of water and 2 fluidounces (59 cc.) of olive oil in 100 cc of water were administered orally.

After the oral administration of 100 gm. of glucose (observation 4), the volume of juice for the first thirty minute period was above average fasting volume (1.7 cc), the volume decreased thereafter, but increased to more than fasting volumes and attained maximal values during the fourth and fifth hours afterward (Table I, Fig. 1). The values for pH increased to high levels, where they were maintained for five hours (Table II). The concentration of bicarbonate gradually increased from 0.07 millimol per cubic centimeter to 0.10 millimol per cubic centimeter in the fourth and fifth hours (Table III). The values for total bicarbonate per unit of time were only moderately elevated above fasting values (0.04 to 0.33 millimol per sample)

TABLE IV
Concentration of amylase in terms of mg of maltose per cc of pancreatic juice

Specimen No	Stimulant Type	Observations																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
		Chemical								E				A	S	S	M	S & M	
		Carbo-hydrate gm	20			100			114	110	113	112	42	63	59				
		Protein gm		10			25		33	27	32	7	51	15	14				
Fat gm			30			60	15	13	16	13	41	37	37						
		Amylase																	
1		34	28	07	28	19			21	17	12		15	17	14		33		
2		31	34	41	24	15	21	10	14	17	22		12	09	07	15	25		
3		31	45	34	24	07		09		17	15		17	09	07		17		
4		48	41	34	24	10		09		15	12		21	10			12		
5		48	48	31	24	12		07	28	21	12		19	12			10		
6				24	15	12	54	09		15	10		21				14		
7					17	15	62	09		15	10		17						
8				31	10	19	76	10	21	19	12								
9				41	10	21		12		14	09								
10					15	21	62	12		19									

Total amylase per sample (concentration times cc)

1	34	41	07	128	170				91	110	48		126	52	70		338
2	28	17	87	67	111	15			78	34	69	68		108	28	32	140
3	28	38	45	53	50				60		71	69		43	19	34	69
4	33	29	107	58	85				62		55	54		41	46		30
5	29	24	31	79	57				76	55	41	41		30	24		35
6			22	54	65	44			77		40	39		31			34
Total	152	149	292	439	539				353		386	319		381	169		646
7				96	62	62			47		39	38		26			
8			19	105	62	57			57	74	39	38					
9			95	88	70				46		25	27					
10				117	32	77			64								
Total				845	764				567		489	422		407			

1 E—Ephedrine sulfate 3/4 grain (H) at start of collection of first specimen

2 A—Atropine sulfate, 1/75 grain (H) at start of collection of first third and fifth specimen

3 S—Secretin 1 clinical unit per kilogram of body weight intravenously

4 M—Acetyl beta methylcholine chloride 15 mg (H)

5 S and M—Combined stimulation by secretin and acetyl beta methylcholine chloride

6 Experiments 1 to 3—Foods given directly into duodenum from which gastric juice was excluded.

7 Experiments 4 to 13—Foods given orally

8 Experiments 1 to 13—All specimens collected over thirty minute periods

9 Experiments 14 to 17—Specimens 1, 2, 3 and 4 collected over ten minute periods; specimens 5 and 6 collected over twenty minute periods.

during the first three hours (0.17 to 0.32 millimol per sample), but were increased markedly in the last two hours (0.50 to 1.02 millimols per sample). The concentration of amylase was constant at 2.4 cc of tenth-normal potassium hydroxide until the sixth thirty-minute period (Table IV), and then decreased (Fig 4) as the volume of juice, concentration of bicarbonate and total output of bicarbonate increased. The value for total amylase was very high (12.8 cc of tenth-normal potassium hydroxide) in the first thirty-minute sample, but the values then decreased about 50 per cent, remained at these levels until the fourth and fifth hours, when they again increased as the volume of juice, concentration of bicarbonate and total output

lipase, the concentration of amylase decreased slightly and that of lipase increased slightly with the increase in the total output of these enzymes. The type of secretion (with the exception of the increase in the concentration of lipase, as noted previously) observed during the fourth and fifth hours resembled that seen after stimulation with purified secretin. The delayed secretin-like effect may be pointed to as the characteristic feature in this observation of the response of the pancreas to stimulation with glucose administered orally.

After the oral administration of 25 gm of casein (observation 5), the volume of juice reached a maximum (9.0 cc) within the first thirty-minute period

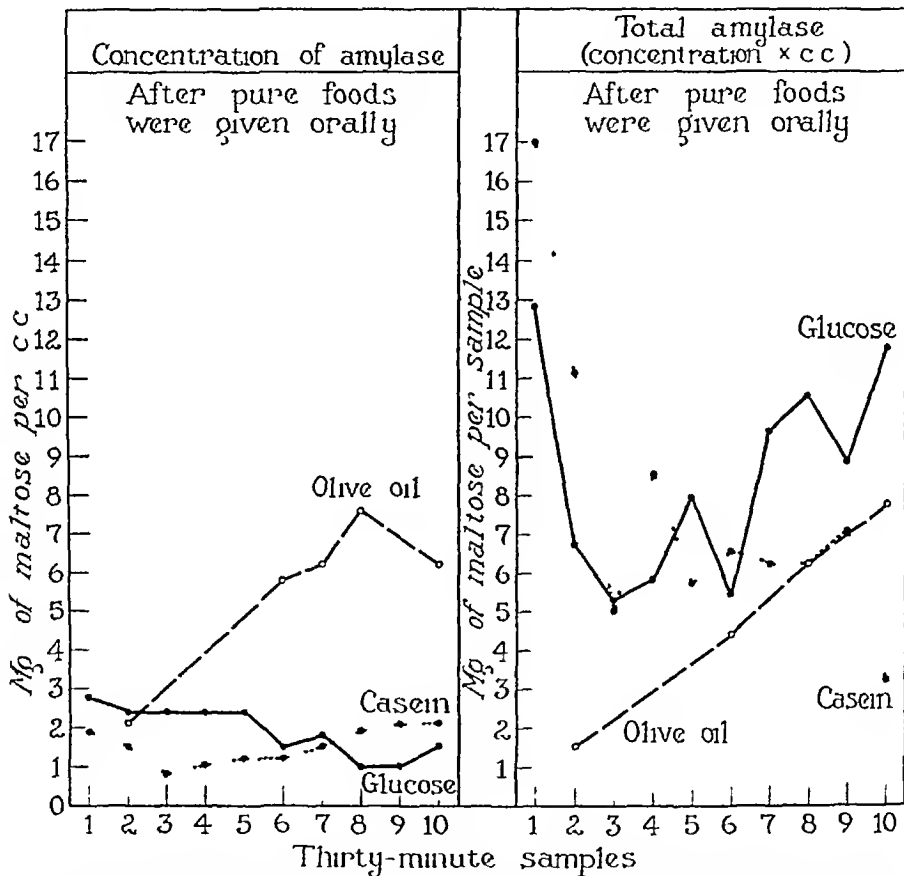


Fig 4 The effect of glucose, casein and olive oil administered orally on the concentration and total secretion of amylase per unit of time in pancreatic juice secreted through an external pancreatic fistula

of bicarbonate increased (Fig 4). Curiously enough, the concentration of lipase decreased instead of being maintained at a more or less constant level, as in the case of amylase, and then increased in the late hours of the experiment instead of decreasing, as in the case of amylase (Table V, Fig 5). The values for total lipase were low after the first thirty-minute samples, until the fourth and fifth hours and then increased (Fig 5), following the typical behavior of volume, concentration of bicarbonate values for total bicarbonate and total amylase. In other words stimulation with glucose administered orally increased the volume of juice (Fig 1), concentration and total output of bicarbonate and total output of amylase and

was maintained at about this level for two hours, then gradually decreased to near basal levels in the tenth thirty-minute period (2.5 cc) (Table I, Fig 1). The values for pH, concentration of bicarbonate, total bicarbonate, total amylase (Fig 4), and total lipase (Fig 5), followed the pattern set by the values for fluid volume (Tables II, III, IV and V). The type of pancreatic secretion in this observation resembled that seen after stimulation with purified secretin, but was more vigorous and prolonged.

Most interesting was the response of the pancreas to the oral administration of 2 fluidounces (59 cc.) of olive oil (observation 6). The volume decreased in the second thirty-minute period and remained low

(Table I Fig 1) Volumes less than average fasting levels were comparable to the very low volumes seen after stimulation with casein and glucose introduced into the duodenum, from which the gastric juice was excluded (observations 1 and 2, Table I) The values for concentration of bicarbonate and total bicarbonate likewise decreased to very low levels (Table III) The concentration of amylase behaved in striking fashion (Fig 4), it gradually increased, reaching levels higher than the high levels noted after stimulation with glucose and casein introduced into the duodenum, from which the gastric juice had been excluded (observations 1 and 2), the total amylase per unit of time behaved in a similar fashion reaching a moderate high level in spite of the low volume of juice secreted (Table IV, Fig 4) The concentration of lipase gradually decreased (Fig 5) Most remarkable was the low total secretion of lipase an observation contrary to what might be expected if olive oil had the specific action of increasing the secretion of lipase (Table V, Fig 5) In this observation olive oil not only failed to stimulate pancreatic secretion, but actually depressed the secretion to less than values obtained under normal fasting conditions (excepting amylase) Stimulation of the secretin mechanism apparently did not occur

Comment—Glucose and casein in these amounts administered orally proved to be vigorous stimulants of external pancreatic secretion Glucose and casein administered orally increased the secretion of fluid volume (Fig 1) increased the concentration of bi-

carbonate and the total amount of bicarbonate, amylase (Fig 4) and lipase (Fig 5) per unit of time The stimulating effects of glucose (Figs 1, 4, 5) were delayed until the fourth and fifth hours, whereas that of casein (Figs 1, 4, 5) was immediate and maximal during the first two hours The pattern of secretion of all these factors was remarkably similar after the administration of either glucose or casein

The concentration of amylase was lowest when the fluid volume was greatest after the administration of both glucose and casein (Fig 4) The concentration of lipase was lowest when the fluid volume was lowest after glucose had been administered orally and was not changed in any direction after casein had been administered orally (Fig 5)

During the first three hours the administration of casein doubled the volume output, trebled the bicarbonate output, increased the total amylase output about 25 per cent and trebled the total lipase output as compared to the action of glucose, whereas during the five-hour period the administration of casein stimulated the volume output only 10 per cent more, the bicarbonate output only 20 per cent more the amylase output only 10 per cent less, and the total lipase output but 30 per cent more than glucose did (Tables I, III, IV and V) Casein in the amount administered proved to be only a slightly more potent stimulant of external pancreatic secretion than glucose Actually, the effect of glucose and that of casein over the five-

TABLE V

Concentration of lipase in terms of cc of twentieth normal sodium hydroxide per cc of pancreatic juice

Specimen No	Stimulant, Type	Observations																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
		Chemical								E				A	S	S	M	S & M
		Carbo-hydrate gm.	20			100		114	110	113	112	42	63	50				
	Protein gm		10			25		33	27	32	7	51	15	14				
	Fat gm			30			60	15	13	16	13	41	37	27				
	Lipase																	
1		186	184	220	220	198				174	188	166		232	176	246		330
2		164	182	238	120	198	208		334	184	174	188		170	156	244	428	262
3		192	198	222	110	170			224		178	186		166	220	276		232
4		184	188	230	108	198			224		184	204		178	396			184
5		148	186	334	120	214			202	204	212	158		168	262			220
6				212	134	182	164		178		212	196		150				192
7					154	192	152		224		180	212		168				
8					184	200	142		250	192	164	172						
9					194	194			284		180	188						
10					186	202	172		276		200							

Total lipase per specimen (concentration times cc)

1	186	276	220	990	1782				777	1222	744			1926	828	1255		1558
2	148	91	500	336	1525	156			2505	460	1051	582		663	507	1122	590	1336
3	173	158	289	242	1241				1568		1467	856		415	484	1352		028
4	109	132	813	259	1624				1613		1178	910		356	1782			460
5	89	93	334	390	1007				2222	408	784	537		260	424			784
6			191	469	93	123			1602		1145	764		225				480
Total	750	705	2347	2686	8161				9510		6837	4393		3854				
7				862	768	152			1434	691	1116	805		252				
8				1877	660	107			1375		1230	550						
9				1649	660				1079		540	564						
10				1866	505	215			1463		600							
Total				8340	10744				14861		10343	6312						

- 1 E—Ephedrine sulfate 3/4 grain (H) at start of collection of first specimen
- 2 A—Atropine sulfate 1/15 grain (H) at start of collection of first, third and fifth specimen
- 3 S—Secretin 1 clinical unit per kilogram of body weight intravenously
- 4 M—Acetyl beta methylcholine chloride 15 mg (H)
- 5 S and M—Combined stimulation by secretin and acetyl beta methylcholine chloride
- 6 Experiments 1 to 3—Foods given directly into duodenum from which gastric juice was excluded
- 7 Experiments 4 to 13—Foods given orally
- 8 Experiments 1 to 13—All specimens collected over thirty minute periods
- 9 Experiments 14 to 17—Specimens 1 2 3 and 4 collected over ten minute periods specimens 5 and 6 collected over twenty-minute periods

hour period was so similar that their action probably should be considered equal in the two observations. On the contrary, reviews of previous observations (8-10) disclose that a carbohydrate diet produced more secretion than did a protein diet. The differences are probably best explained on the basis of differences in foods used and duration of the observations.

The effect of olive oil administered orally on external pancreatic secretion was entirely different from the effect of either glucose or casein administered orally. Glucose and casein stimulated the secretion of fluid volume, bicarbonate, amylase and lipase but olive oil did not provoke any such effect. The values for fluid volume, concentration of bicarbonate, total bicarbonate and total lipase rapidly decreased after the ingestion of olive oil to the very low levels noted in the fasting state, and remained there for the duration of the observations.

Purified secretin administered intravenously produces a rapid increase in fluid volume of pancreatic secretion in the concentration and total secretion of bicarbonate and in the total secretion of amylase, trypsin and lipase, but reduces the concentration of enzymes during the period when fluid volume is greatest (1, 4, 7). Glucose and casein administered orally produced exactly the same secretory response in these observations. In fact, the secretory response of the pancreas to glucose and casein administered orally was so similar to that evoked by purified secretin that it appears that acid gastric contents, by means of their effect on the secretin mechanism and not the foods acting directly on the pancreas, determined the response. The food apparently determined the time of the response. Casein provoked an immediate response, glucose a delayed response. It has been suggested (10) that the delay in the appearance of maximal se-

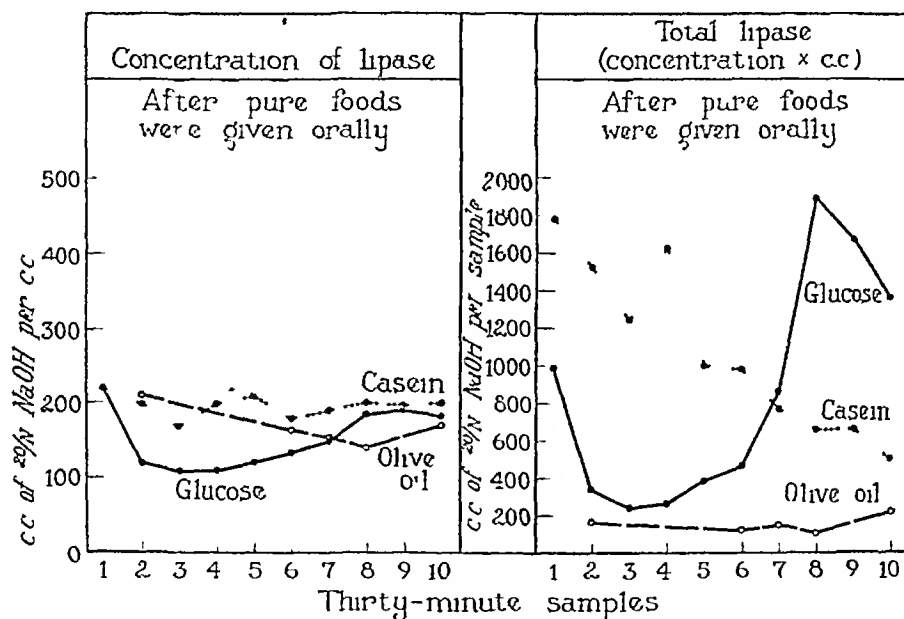


Fig 5 The effect of glucose, casein and olive oil administered orally on the concentration and total secretion per unit of time of lipase in pancreatic juice secreted through an external pancreatic fistula.

The contrasting behavior of the concentrations of lipase and amylase after the oral administration of olive oil is of interest. The concentration of lipase decreased but curiously enough, the concentration of amylase increased and reached levels seen only during observations in which the gastric secretions were prevented from entering the duodenum and in which pure food was introduced directly into the duodenum through the duodenal tube. An increase in the values for total amylase paralleled the increase in the values for the concentration of amylase.

The volume and output of bicarbonate, lipase and probably amylase which followed the oral administration of olive oil were much smaller than those which followed the administration of glucose and casein, although the output of amylase after the administration of olive oil was much nearer the output of amylase after glucose and casein had been administered than were the volume and output of bicarbonate and lipase (see totals in Tables I, III, IV and V).

cretion after the taking of glucose may be related somehow to the delayed emptying time of the stomach brought about by the hypertonic nature of the solution of glucose described by Shay and Gershon-Cohn (9).

The effect of olive oil when it was administered orally on pancreatic secretion was totally dissimilar to the effect of glucose and casein. The features characteristic of stimulation with purified secretin so clearly noted after the giving of glucose and casein were totally missing. The absence of a secretin-like effect suggested that gastric juice did not enter the duodenum, either because of suppression of the gastric secretion or gastric emptying by the olive oil. The observations made in dogs by Farrell and Ivy (11) may be pertinent in explaining the effect of olive oil as just noted. These authors demonstrated that olive oil reduces gastric secretion during the first and second hours after it is administered, but they also found that olive oil increases gastric secretion during the third and fourth hours.

The concentration of amylase after the giving of olive oil attained values greater than those observed elsewhere in observations 1 to 6 inclusive. The increase in values occurred as the volume of juice decreased to a very low level, suggesting that the high values were to some extent due to the concentration brought about by a low volume of secretion. A similar explanation for the high values for concentration of amylase has been suggested in observations 1, 2 and 3 in which the same combination of low volumes and high values for concentration of amylase were encountered.

It is curious that the administration of olive oil should have been followed by an increase in the concentration of amylase (Fig. 4) and not of lipase (Fig. 5). It is doubtful that olive oil has a specific stimu-

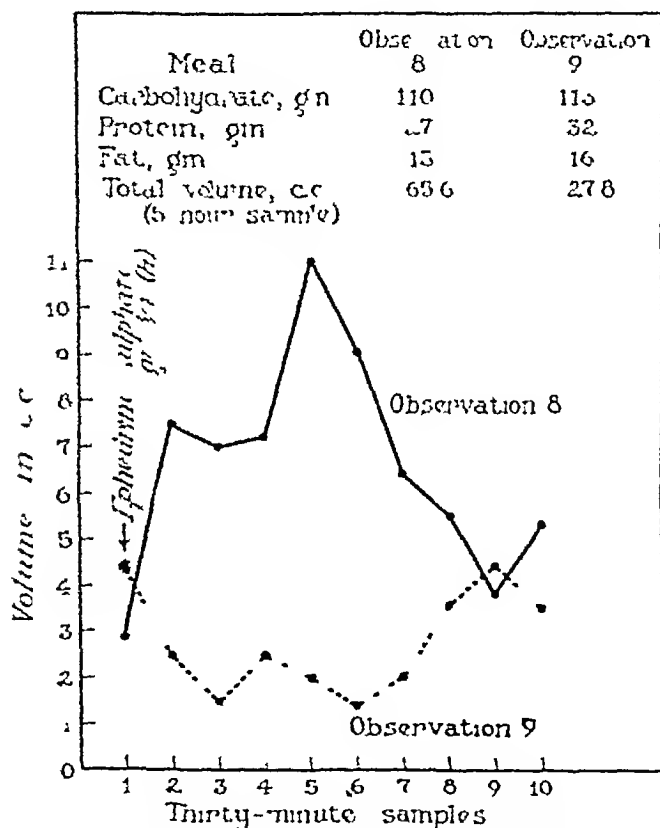


Fig. 6. The effect of ephedrine sulfate (H) on the volume of pancreatic secretion, induced by a meal and secreted through an external pancreatic fistula.

lating effect on the concentration of amylase. It did not show any greater effect on the concentration of amylase than did glucose and casein in the observations in which gastric juice was excluded from the duodenum and in which the food was introduced directly into the duodenum (observations 1, 2 and 3).

The contrast in behavior of pancreatic secretion after stimulation with pure foods introduced into the duodenum, from which the gastric juice had been excluded, and after stimulation with pure foods fed orally, was instructive to us (Fig. 1). The first type of stimulation produced little secretion, regardless of the food used, the second produced a copious secretion rich in all the factors studied when glucose and casein were used, and but little secretion when olive oil was used. Pancreatic secretion was minimal when gastric juice was excluded mechanically from the duodenum or when gastric juice presumably was excluded by the

physiologic effect of olive oil. Secretion was increased whenever the gastric juice entered the duodenum. The contrast in the magnitude of the values obtained with and without stimulation with gastric juice leaves little doubt as to the relative importance of gastric juice and of glucose, casein and even of olive oil in producing the secretion not only of water and alkali but also of enzymes in this individual. Gastric juice certainly appeared to be more potent than food in this respect.

Secretion after the ingestion of mixed foods—The volume of pancreatic juice secreted during a twenty-four hour period was measured. It totaled 212.6 cc. During the twenty-four hour period the patient was given breakfast containing approximately 60 gm of carbohydrate, 15 gm of protein and 37 gm of fat, lunch consisting of about 114 gm of carbohydrate, 30 gm of protein and 15 gm of fat and dinner of similar proportions.

High carbohydrate, high protein, low fat meals were fed in observations 7 and 8; a high carbohydrate, low protein, low fat meal was fed in observation 10; a low carbohydrate, high animal protein, high fat meal was fed in observation 11; and relatively low carbohydrate, low protein, high fat meals were fed in observations 12 and 13. The values for carbohydrate, protein and fat are given in grams in each table.

Perusal of the data (Tables I to V, observations 7, 8, 10, 11 and 12) discloses that the total volume of juice and values for total bicarbonate, total amylase and total lipase after stimulation with the high carbohydrate, high protein, low fat meal in observations 7 and 8 are not different from the volume and values for total bicarbonate, amylase and lipase after stimulation with a meal containing almost identically the same amount of carbohydrate and fat but almost no protein (observation 10). Pancreatic secretion seemed to be slightly greater after the high carbohydrate, low fat meal containing much protein (observations 7 and 8) than after the ingestion of a high carbohydrate, low fat meal containing little protein (observation 10). More interesting are the definitely greater volume and values for total bicarbonate, total amylase and total lipase obtained after ingestion of the high carbohydrate, high protein, low fat and high carbohydrate, low protein, low fat meals (observations 7, 8 and 10) than after ingestion of the low carbohydrate, high protein, high fat meal in experiment 11. The large amount of fat in the low carbohydrate, high protein, high fat meal (observation 11) seemed to neutralize the effect of protein and measurably to diminish the secretion. This effect of fat was not unexpected in view of the effects of olive oil obtained in observation 6. Curiously enough, the same amount of fat in the meal given in observation 12, in which there was a greater amount of carbohydrate and little protein, did not suppress secretion. In this experiment the volume increased promptly to high levels.

The concentration of amylase was low in the first thirty-minute specimen and became lower after ingestion of the high carbohydrate, high protein, low fat meal (observation 8); was low and became slightly lower after ingestion of the low carbohydrate, high protein and high fat meal (observation 11), but was high and was not definitely increased or decreased after ingestion of the high carbohydrate, low protein, low fat meal (observation 10).

The concentration of lipase was, on the average, higher after the ingestion of a high carbohydrate, high protein low fat meal (observation 8) than after ingestion of high carbohydrate, low protein, low fat (observation 10) and low carbohydrate, high protein, high fat meals (observation 11) the concentration fluctuated in no definite direction. In general, the action of the mixed meal was determined by the foods predominating in the meal, the high carbohydrate or high protein meals producing more secretion than a high fat meal.

The effect of ephedrine sulfate on the secretion of the pancreas—Ephedrine sulfate in a dose of $\frac{3}{4}$ grain (0.05 gm) (Fig 6) was administered subcutaneously in observation 9 at the start of ingestion of a high

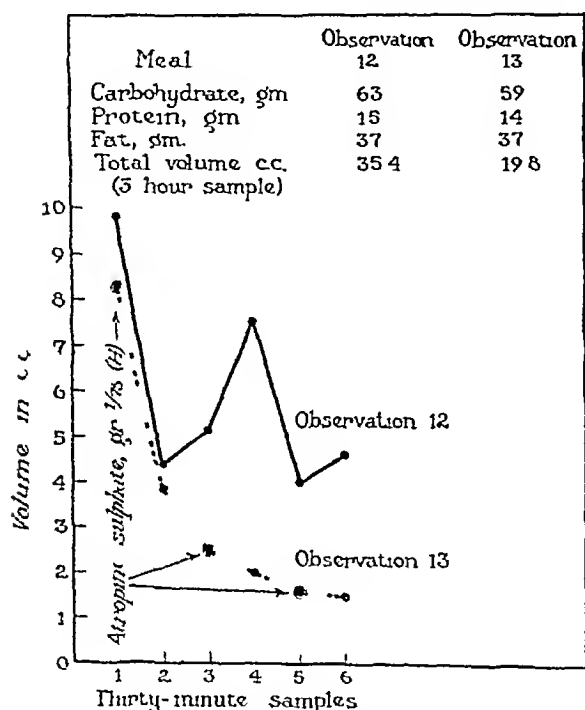


Fig 7 The effect of atropine sulfate on the volume of pancreatic secretion induced by a meal and secreted through an external pancreatic fistula

carbohydrate, high protein, low fat meal similar to that given in observations 7 and 8. The volume of juice secreted in the five-hour period after ingestion of a meal and the administration of ephedrine sulfate was approximately 50 per cent less than it had been in the five hours after ingestion of a meal without the administration of ephedrine sulfate. Although the data are incomplete in so far as bicarbonate, amylase and lipase are concerned, comparison of the data for corresponding thirty-minute periods when ephedrine sulfate was and was not given, likewise indicates that ephedrine sulfate decreased the values for concentration and total bicarbonate did not markedly affect the values for concentration of lipase but decreased the value for total lipase and increased the concentration of amylase but did not affect the total output of amylase so far as can be judged. In short, ephedrine sulfate reduced the volume of juice total output of bicarbonate and lipase, but did not appreciably

affect the output of amylase in this observation. Craft (12) has concluded that ephedrine sulfate given subcutaneously decreases the volume of pancreatic juice, just as epinephrine does probably by means of its inhibitory effect on the secretion of pancreatic juice through the vasoconstrictive action on the blood vessels of the pancreas, resulting in a decrease in the minute volume flow of blood to the pancreas and a decrease in the secretion of pancreatic juice.

Effect of atropine sulfate on the external secretion of the pancreas—Atropine sulfate in a dose of 1/75 grain (about 0.0009 gm) (Fig 7) was administered subcutaneously in observation 13, at the beginning of the meal and again at the end of the first and of the second hour after the ingestion of the meal. In observation 12, an identical meal was fed and atropine sulfate was not administered, in order to furnish data for comparison. However, because of error, the only data secured in this observation were the volume of secretion for each thirty-minute period. Comparison of the data from observation 13, in which atropine sulfate was given, with data from other observations, in which atropine sulfate was not given, shows that the volume of secretion and the values for pH, concentration and total bicarbonate of each specimen were unaffected in the first hour, but were reduced in the second and third hours after the start of the experiment. Atropine sulfate did not appreciably affect the concentration or total output of amylase, but reduced slightly those of lipase.

Atropine sulfate reduced that part of the secretion stimulated particularly by the secretin mechanism. Observers agree that atropine sulfate reduces the volume of pancreatic secretion. Its effect is not a direct but an indirect one on the secretin mechanism through its reduction of gastric motility and secretion as has been shown by Farrell and Ivy (11) and others.

Effect of purified secretin and mechohyl chloride on the external secretion of the pancreas—Purified secretin was administered intravenously in doses of 1 clinical unit for each kilogram of body weight and mechohyl chloride (acetyl methylcholine chloride) was administered subcutaneously in doses of 15 mg to the patient after a twelve-hour fast. The secretion was collected first in four fractions of ten minutes each, and then in two fractions of twenty minutes each.

Secretin produced a large volume of secretion, with a high pH, a high concentration of bicarbonate and a high total bicarbonate per fraction. The concentration of amylase decreased in the second and third fractions. The total secretion of amylase was greatest in the first ten-minute specimen after stimulation. In these respects the secretion of pure pancreatic juice from the fistula behaved in a fashion similar to that of the pancreatic secretion collected from the duodenum, from which the gastric juice had been excluded (1, 7).

The behavior of lipase failed to follow a definite pattern in these two experiments, as it may fail to do when this secretion is collected from the duodenum, from which gastric juice is excluded.

Rough comparison of the maximal values for volume, pH, bicarbonate and enzymes in juice collected from the fistula after stimulation with purified secretin and after stimulation with pure foods or mixed meals is instructive. To do this, the sum of the values for the first three fractions of ten minutes each, after the administration of secretin is compared with the maxi-

mal values for a thirty-minute period, after ingestion of a meal. The maximal thirty-minute volume after the administration of secretin was about 50 per cent greater than the greatest volume encountered in any thirty-minute period (specimen 5, observation 8) after the ingestion of food. The maximal value in the thirty-minute specimen after the administration of secretin was for bicarbonate, about 50 per cent greater, for amylase 20 per cent less for lipase, about 70 per cent greater than the greatest values obtained in any thirty-minute specimen after the ingestion of food (specimen 4, observation 5, in the case of carbonate, specimen 1, observation 5, in the case of amylase, specimen 2, observation 8, in the case of lipase). As a stimulant of pancreatic secretion, the preparation of secretin used, in doses in which it was given intravenously, is in a general way as potent or slightly more potent than food given orally but its effects are of much shorter duration.

After the administration of mecholyl chloride, the volume of secretion obtained from the fistula for each ten-minute period was very small, the concentration of bicarbonate was moderate. The values for volume, concentration and total bicarbonate were similar to those of the fasting secretion, both with and without the gastric juices entering the duodenum. As previously reported (7) mecholyl chloride had no great effect on the secretion of fluid and bicarbonate. McCaughan, Sinner and Sullivan (8) found, on the contrary, that mecholyl chloride given by cataphoresis is more of a stimulant of volume output than is purified secretin, water, beef broth, olive oil, dextrose, mixed meal, hydrochloric acid, peptone, physostigmine or pilocarpine hydrochloride. Its action presumably is due to stimulation of the parasympathetic nerve fibers supplying the pancreas.

After stimulation with secretin and mecholyl chloride combined, the values for volume, pH and bicarbonate were similar to those obtained after stimulation with secretin alone whereas the values for amylase and lipase were greater than those for secretin alone. If the sum of the values for the first three ten-minute periods after stimulation with secretin plus mecholyl is compared to maximal values for any thirty-minute period after stimulation with foods, it is seen that secretin plus mecholyl is a somewhat more potent stimulant of volume output, total bicarbonate, total amylase and total lipase than are foods, but that the effect is less prolonged. The combination of purified secretin and mecholyl chloride as a stimulant of external pancreatic secretion produces greater values for all components of external pancreatic secretion than do foods or secretin given alone as previously reported (13).

CONCLUSIONS

A case of external pancreatic fistula in which cure was effected surgically has been reported. Certain physiologic observations were made.

The fasting secretion of pancreatic juice through the external fistula, when the pancreatic juice was excluded from the duodenal cavity, was low in volume and in total bicarbonate and enzyme content.

The fasting secretion of pancreatic juice through the external fistula, when the gastric juice was allowed to enter the duodenal cavity, was variable but, for the most part was low in volume and bicarbonate content.

The secretion of pancreatic juice through the external fistula, when gastric juice was excluded from the duodenum, was not measurably stimulated by glucose and casein and was only slightly stimulated by olive oil introduced through the duodenal tube into the duodenum.

Secretion of pancreatic juice through the external fistula was stimulated vigorously by glucose and casein administered orally. The effect of glucose and casein was similar to that obtained by administration of purified secretin. They effected an increase in volume and an increase in the total secretion of bicarbonate, amylase and lipase, just as purified secretin does. The secretion of pancreatic juice through the external fistula and its content of bicarbonate and lipase was not stimulated and was probably depressed by olive oil administered orally, the secretion of amylase, on the contrary, appeared to be mildly stimulated. The type of secretory response of volume of bicarbonate and of enzymes seemed to depend, first, on the gastric secretory response to food and emptying time of the stomach and, second, on the effect of gastric secretion on the secretin mechanism. The type of secretory response did not appear to depend as much on the effect that food exerts directly on pancreatic secretion as on the effect of foods on gastric secretion. Gastric contents (gastric secretion plus food) was a much more potent stimulant of pancreatic secretion than were foods alone.

The secretion of pancreatic juice through the external fistula after the administration of mixed meals depended on the proportion of the different foods present in the meal. Meals low in fat and high in carbohydrate and protein stimulated a greater flow of all components of the pancreatic juice than did meals high in fat.

Ephedrine sulfate and atropine sulfate decreased the fluid volume and values for total bicarbonate and lipase, but did not materially diminish the total amylase values of pancreatic juice secreted through the external fistula. Secretin in the doses given appeared to be equal to or somewhat more potent than did the normal secretin mechanism stimulated by a meal in producing secretion of pancreatic juice for each unit of time. Mecholyl chloride (acetyl methylcholine chloride) did not appreciably increase the secretion of fluid volume or bicarbonate to more than fasting values. Secretin plus mecholyl chloride evoked a greater secretion of all components of external secretion than did any other stimulant used.

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The External Secretion of the Pancreas and Diabetes Mellitus*

By

H M POLLARD M.D., LILA MILLER Ph.D.

and

W A BREWER, B.A.

ANN ARBOR MICHIGAN

SINCE purified secretin has become commercially available data on the composition of the pancreatic juices in healthy and pathological subjects have been accumulating. The results obtained for diabetic subjects are rather limited and are not entirely consistent. Of the pancreatic juices from the four diabetic subjects used by Agren, Lagerlof and Berglund (1) two were normal with respect to the values for volume, and for concentrations of bicarbonate, trypsin and amylase. However, the third subject had a low concentration of bicarbonate and the fourth a low secretion of amylase. These deviations in the third and fourth cases could be correlated with severe cholangitis and jaundice in one and acute pancreatitis with jaundice in the other.

The observations of Diamond and his coworkers (2) were similar. Of the four cases studied, two had low values for the bicarbonate in the pancreatic juice, one a low lipase and one was normal in all respects. The complications of gall stones in two of these subjects and acute edema of the pancreas in the third may have affected the composition of the duodenal pancreatic secretion. Similar deviations in the composition of these juices were observed in three of the six diabetic subjects used as a part of a larger study and reported recently from this laboratory (3). The volumes of secretion and the total bicarbonate, amylase and trypsin in these three cases were less than those of the control group.

These observations seemed to warrant a more extended study of the results of the application of the secretin test to diabetic patients. Our own group has now been increased to 13 and the results are presented in this paper.

EXPERIMENTAL

The subjects of this study were 13 patients in the University of Michigan Hospital who had unquestioned diabetes mellitus. The test was performed in the manner previously described after a 12 hour fast and with the use of one clinical unit of secretin† per kilogram of body weight. The combined duodenal-pancreatic juices and the gastric juice were withdrawn continuously but separately through a soft rubber double lumen tube. The time of collection comprised

of two 20-minute periods prior to the intravenous administration of the secretin and four consecutive periods afterwards, the first two of 10-minutes duration and the last two of 20-minutes duration. The volume, pH, bicarbonate and Meulengrecht number of each of the samples thus obtained were determined. Likewise in the first six cases, the tryptic and amylolytic activities were also estimated in the individual samples. However, in the last seven cases the procedure was changed as the total secretion of enzymes and not the concentration in each sample had been found significant. A pooled juice representative of the total secretion was obtained by mixing aliquots which were proportional to the respective volume of each sample collected after the administration of secretin. In this way the number of determinations were decreased and sufficient material was always available for duplicate determinations. The analytical procedures were the same as described previously (3).

The analytical data are presented in Table I and the relevant clinical data in the clinical notes. The ages of the subjects range from 10 to 64 years, ten being under 30 years and three over 45. The period of known duration of the disease in these subjects varied from less than one year to 17 years. In one instance the secretin test was given the day after the diabetes had been diagnosed.

Definite abnormalities in the composition of the duodenal-pancreatic juices were found to occur where the known duration of the disease had been of 3 or more years. Every subject who had had diabetes 3 years or longer showed two or more deviations when compared with the control group reported in the previous paper (3). Of the eight diabetics constituting this group (cases 43, 11, 44, 10, 35, 36 and 13) six had a diminished or borderline volume of secretion, five a low value for the maximum concentration of bicarbonate and seven a low total secretion of bicarbonate. As pointed out previously (3), the total secretion of bicarbonate for the entire period of collection is a better index than the maximum concentration of bicarbonate of a single specimen collected during the test period. Likewise the amylase activity was either borderline or distinctly low in seven instances. The data for the tryptic activity are not complete because in two instances the volume of some of the samples had been too small to permit determination. However, three of the six cases for which we

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†Pancreo-test, Astra, Sdertälje, Sweden.

From the Departments of Internal Medicine and Biological Chemistry, University of Michigan Medical School.

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have complete data on the tryptic activity had a diminished secretion of trypsin.

Of this group of eight who had had the diabetes 3 years or longer, the two subjects who exhibited the least deviations from our group of normals were cases 35 and 44. The latter was considered to be a mild diabetic and the disease was known to have been present for 5 years. In case 35 the absence of gall bladder function may have been responsible for the apparently normal volume of secretion and bicarbonate accompanied by borderline values for the two enzymes. The hepatic bile would augment the values for both the volume and the bicarbonate without affecting the values for the total secretion of enzymes. This effect of the free flow of hepatic bile was noted in a previous study of eight cases of gall bladder disease (3). Thus only one instance of borderline values for trypsin—amylase were observed and all the values for volume and bicarbonate were above the minimal figures for the control group. Hence the borderline values in case 35 might be attributed to the diabetes mellitus. The diagnosis of cholecystitis in case 35 had been made on the basis of symptoms.

The remaining five cases (38, 41, 5, 16 and 42) had had diabetes 15 years or less. In this group only one subject, case 41, exhibited a diminished secretion of bicarbonate and enzymes. The volume of secretion was slightly above the minimal value for the control group. That this patient was still excreting sugar and had a high fasting blood sugar at the time of his dismissal from the hospital 3 weeks later may be significant.

These deviations observed, using the control group

as the standard, could not be correlated with the age of the subjects, the blood sugar level, the presence or absence of acidosis at the time the secretin test was performed, the diet or the amount of insulin being administered.

DISCUSSION

The subjects used in this study had been selected only insofar as to give a wide range in the age of the patients, in the severity of the disease and in its duration. Furthermore, they were singularly free of other gastro-intestinal disturbances with the exception of three cases. Two had mild chronic cholecystitis, one without stones (case 35) and one with stones (case 16), and the third case had steatorrhea (case 15). The other ten were entirely free of symptoms and signs of any gastro-intestinal disturbance. The absence of biliary disease in these ten subjects therefore stands in marked contrast to similar experiments on diabetics as reported by other authors. While the total number of cases is small, nevertheless the fact that the duration of the disease was the only condition which could be correlated with the deviations observed seems significant.

These results are in part similar to those obtained by Jones and his group (4) in their extensive study of pancreatic secretion of diabetic subjects. They found that a diminished enzyme activity in 49 per cent of the 68 patients could not be correlated with fasting blood sugar levels or severity of the disease. However, the duration of the disease did not appear to be related to the abnormal enzymatic activity. In that in-

TABLE I

Composition of duodenal-pancreatic juices obtained from individuals with diabetes mellitus following injection of secretin

Case	Sex	Age	Duration of Disease	Volume Per Kg Body Wt	Maximum pH	Bicarbonate		Trypsin Per Kg Body Wt	Amylase Per Kg Body Wt
						Maximum Concentration	Per Kg of Body Wt.		
		Yrs	Yrs	cc		m eq Per l	m eq	Units†	Units‡
35	M	23	0	16	8.28	143	0.18	2.1	633
41	M	17	0.17	0.8	7.63	70*	0.05*	4.5	887*
5	F	53	<10	2.4	8.46	111	0.18	9.0	1285
16	F	46	<10	1.9	8.19	97	0.13	3.0	910
42	M	10	15	2.9	8.03	82	0.14	11.7	904
48	M	20	3	0.1*	8.55	73*	0.05*	1.2*	104*
11	F	21	4	0.7*	7.60	30*	0.01*	10.4	166*
44	M	64	5	1.2	8.05	50*	0.04*	2.0	702
10	M	17	7	0.4*	8.75	120	0.02*	—	135*
35	M	23	8	2.0	8.01	06	0.12	1.4*	543*
15	M	27	10	0.5*	8.59	65*	0.02*	3.4	491*
36	M	20	11	0.5*	8.54	105	0.03*	0.3*	94*
13	F	25	17	0.4*	8.72	62*	0.04*	—	594
Control Group									
Minimal values				0.7	7.42	75	0.03	1.0	325
Maximal values				2.6	9.06	141	0.15	13.2	2848

*One unit of trypsin designates that quantity of enzyme which effects a hydrolysis of a casein buffer substrate under given conditions corresponding to 0.250 cc of 0.1 N sodium hydroxide (3).

‡The unit of amylase is the reducing substances expressed as milligrams of glucose produced by the action of 1 cc of the juice on a starch substrate under given conditions (8).

*Indicates an abnormal or borderline value on the basis of the control group (3).

vestigation magnesium sulfate and cream were used in place of secretin, and the samples were collected through a single lumen tube

No necropsy material was available from any of these cases and hence direct correlation of the histological changes of the pancreas was impossible. However, the lack of any characteristic histological changes in the pancreas of diabetic patients as reported in the literature is striking. The pancreases of the juvenile diabetic patients and those of adults who have had the disease but a short time exhibit few or no abnormalities regardless of the severity of the disease (5). One of the changes which might be correlated with the diminished secretions reported here is the presence of fibrous tissue so that sometimes the acinar tissue almost completely disappears particularly when it centers about the duct (6). Warren also claims that in instances of severe hyalinization or fibrosis of the islands at least a moderate degree of interacinar fibrosis is always found. Furthermore acinar sclerosis is not apparent in cases much under two years duration (7).

According to recent work the bicarbonate ions in the pancreatic juice of dogs are believed to originate chiefly from the bicarbonate ions of the plasma and not from the metabolic carbon dioxide of the cells of the gland (8). The use of radio active carbon, C^{14} , made this differentiation possible. The bicarbonate ions pass freely both into and out of the cells of the pancreas whereas the chloride ions do not pass out readily and thereby may regulate the bicarbonate concentration of the juice. Therefore, the diminished secretion of bicarbonate and enzymes supported by the apparent origin of the bicarbonate ions and the histological changes noted above suggests that the acinar tissue is affected when diabetes mellitus is of long duration.

SUMMARY

1 Thirteen subjects with diabetes mellitus were used in a clinical study of the secretin test.

2 The observed deviations from the control group of four patients were diminutions in volume of secretion and total secretion of bicarbonate and the enzymes amylase and trypsin. With one exception these changes were confined exclusively to those patients who had the disease for 3 years or longer.

3 These abnormalities of the duodenal-pancreatic juice could be correlated only with the duration of the disease and not with the age of the patient, the severity of the disease, the presence or absence of acidosis, the amount of insulin required or the diet.

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CLINICAL NOTES

Case 28. Secretin test 3-13-41 Urine 3-12, sugar + + + + acetone + + +, acetoacetic acid + + +, 6 a.m.

3-13, entirely normal. Fasting blood sugar 3-12, 324 mg per cent, 3-18, 136 mg per cent. CO_2 capacity 3-12 42 vol. per cent. Insulin 3-12, 60 units of regular. Diet 90 gm of protein, 250 gm of carbohydrate, 3000 calories. No dietary regimen nor insulin treatment had been instituted prior to admission to the hospital. Sodium bicarbonate, 20 gm doses, was administered at 7 and 9 p.m., 3-12 and 6 a.m. 3-12.

Case 41. Secretin test 3-27-41 Urine 3-26, urine + + + +, acetone + + + + 3-27, sugar +, acetone + +, 3-28, sugar + + + +, acetone 0. Fasting blood sugar 3-26, 290 mg per cent. CO_2 capacity 3-26, 34 vol per cent. Insulin 3-26, 60 units of regular. Diet 80 gm of protein, 150 gm of carbohydrate, 1800 calories. The urinary sugar on 4-19, the date of dismissal, was + +, the fasting blood sugar 194 mg per cent, and the insulin administered was 55 units of protamine-zinc insulin and 35 units of regular. Skull X-rays Normal.

Case 5. Secretin test 11-29-39 Urine 11-28, sugar + +, 11-29, sugar + +, 11-30, sugar 0. Fasting blood sugar 11-28, 220 mg per cent, 2-1-39, 176 mg per cent. Insulin 11-28, 120 units of regular and 20 units of protamine-zinc insulin. Diet 80 gm of protein, 150 gm of carbohydrate, 2400 calories. The subject was admitted 11-20 in a state of coma.

Case 16. Secretin test 2-21-41 Urine 2-20, sugar + + +, 2-23, sugar + + +. Fasting blood sugar 2-26 222 mg per cent. Insulin 2-20, 30 units of regular. Diet 80 gm of protein, 200 gm of carbohydrate, 2800 calories.

Case 42. Secretin test 3-31-41 Urine 3-30, sugar + + +, 3-31, sugar + + + +, 4-1, sugar + + +, no acetoacetic acid. Insulin 3-30, 52 units of regular. Diet 85 gm of protein, 105 gm of fat, 230 gm of carbohydrate 2200 calories. The subject was admitted 3-9 in a state of acidosis due to disregard to dietary instructions.

Case 43. Secretin test 4-14-41 Urine 4-13 sugar + + + + 4-14, sugar 0, 4-15, sugar + +. Sugar free thereafter. Fasting blood sugar 4-3, 254 mg per cent, 4-18, 80 mg per cent. Insulin 4-13, 25 units of regular and 35 units of protamine-zinc insulin. Diet 90 gm of protein, 200 gm of carbohydrate, 2800 calories.

Case 11. Secretin test 1-24-40 Urine 1-23, sugar + + + +, 1-24 sugar + + + +, 1-25, sugar + + + +. Fasting blood sugar 1-22, 217 mg per cent. Insulin 1-23, 90 units of regular and 40 units of protamine-zinc insulin. Diet 80 gm of protein 200 gm of carbohydrate 3000 calories. Basal metabolic rate 1-24, +30 1-26 -29.

"patient's diabetes might be on a pituitary basis, which could explain the high B.M.R. and the insulin resistance." Skull X-ray Negative.

Case 44. Secretin test 4-16-41 Urine 4-15, sugar + +, 4-16, sugar + + + +, 4-17, sugar + +. Insulin 4-15, 20 units of regular. Diet 80 gm of protein, 150 gm of carbohydrate, 2600 calories. Discharged 4-18. Considered a mild diabetic, able to get along with 5-10 units of regular insulin morning and evening with a 2400 calorie diet.

Case 10. Secretin test 1-15-40 Urine 1-14, sugar + + + + acetone 0, 1-15, sugar + + + +, acetone + 1-16 sugar + + +, acetone +. Fasting blood sugar 1-18, 190 mg per cent. Insulin 1-14, 70 units of regular and 30 units of protamine-zinc insulin. Diet 90 gm of protein 150 gm of carbohydrate, 2800 calories.

Case 35. Secretin test 2-26-41 Urine 2-25 sugar + + + +, 2-26, sugar + + + + 2-27, sugar + + + +. Fasting blood sugar 2-19, 282 mg per cent, 2-25, 68 mg per cent, 2-27, 60 mg per cent. CO_2 capacity 2-19, 40 vol per cent. Insulin 2-25, 65 units of protamine-zinc insulin. Diet 90 gm of protein 200 gm of carbohydrate 2600 calories.

Case 15. Secretin test 2-18-40 Urine 2-17, sugar + + + + 2-18 sugar + + + +, 2-19 sugar + + + +. Fasting blood sugar 1-10, 410 mg per cent, 2-27, 468 mg per cent. Insulin 2-17, 47 units of regular. Diet 125 gm.

of protein, 146 gm of fat, 250 gm of carbohydrate, 2800 calories. The subject had been in coma at least once.

Case 36 Secretin test 3-3-41 Urine 3-2, sugar ++, 3-3, sugar ++, 3-4, sugar +. Fasting blood sugar 2-14, 150 mg per cent, 3-9, 272 mg per cent. Insulin 3-2, 55 units of regular. Diet 100 gm of protein, 201 gm of fat, 200 gm of carbohydrate, 3000 calories.

Case 13 Secretin test 2-12-40 Urine 2-11, sugar +, 2-12, sugar trace, 2-13, sugar ++. Fasting blood sugar 2-9, 270 mg per cent, 2-12, 232 mg per cent. Insulin 2-11, 30 units of regular and 40 units of protamine-zinc insulin. Diet 60 gm of protein, 150 gm of carbohydrate, 1400 calories.

DISCUSSION

DR LEMUEL C MCGEE (Wilmington, Del.) I think any approach to the secretion of the small bowel which should give us information regarding the electrolyte or enzyme content, is quite important.

I was impressed by the change which was found in those older diabetics of the two groups, the bicarbonate content.

Several years ago Carr and Abbott, using the Miller-Abbot tube in intubation, demonstrated a certain reciprocal relationship between bicarbonate and the chloride content. They represent the two chief negative ions.

Subsequently, in some work which was published by Dr Emery and myself, and by Dr Hastings and myself, it was demonstrated that these two negative ions not only were reciprocal, as previously indicated by Carr and Abbott, but maintained a fairly constant pH in the upper small bowel.

I would question the advisability of attaching too much significance to a low bicarbonate content unless the chloride was determined at the same time. If he has the chloride observations, I should be interested to hear his comment upon this reciprocal relationship of which I am sure he is aware.

DR H MARVIN POLLARD (Ann Arbor) (closing the discussion) In answer to Dr McGee's question, we did not determine the chloride content. We did determine the free acid in the gastric contents, but there was no determination made of the chloride content in the duodenum.

The Gastric Mucosa, "Gastritis" and Ulcer

By

STEWART WOLF*

and

HAROLD G WOLFF

NEW YORK NEW YORK

STUDIES have been pursued on a 57 year old subject with a large permanent gastric fistula 3.5 cm in diameter surgically produced in 1895 because of benign stricture of the oesophagus. The mucosa lining the stomach has been examined by direct inspection and gastroscopically, and has been found to be of normal appearance. Likewise secretory and motor functions have been studied and found to be undisturbed (1). The present communication deals with an investigation of changes in appearance of the gastric mucosa of this individual after various stimuli.

Since the advent of gastroscopy there has been much interest in certain deviations from the usual appearance of the stomach mucosa called "gastritis". The changes have been classified by various observers and morbid symptoms have been attributed to some of them (2, 3, 4).

Beaumont (5) was among the first to describe the clinical appearance of "gastritis". He called attention to unusual redness or pallor of the mucous membrane of St Martin's stomach accompanied by small lesions which appeared pustular or more commonly greyish crusts which he called "aphthous spots". His descriptions are not detailed enough to enable the present day reader to visualize exactly what he saw. In fact, he usually merely noted that the stomach was of a "morbid appearance," and that most often after what he considered excessive eating or drinking of spirituous liquors on the part of his subject.

The "aphthous spots" which Beaumont noted have

already been discussed elsewhere (1), and it appears possible that he referred to flecks of rolled up precipitated mucus which adhered in places to the lining of the stomach.

The occurrence of pustular lesions in the mucous membrane of the stomach has never been confirmed by subsequent observers and it is likely that in the face of the unsatisfactory lighting conditions and other difficulties of seeing clearly into his subject's stomach, with which Beaumont had to contend, he misinterpreted the appearance of some of these mucus flecks as pustular. It is noteworthy that nowhere does he mention actually having recovered pus from one of them.

As for the "abnormal" redness or pallor of the mucosa which Beaumont observed, we have shown elsewhere (1), that profound color changes occur in the gastric mucosa in the absence of disease and in association with varying day to day conditions which must be regarded as normal.

It appears, then, that there is some doubt as to whether color changes and the appearance of localized spots on the stomach lining represent disease or "gastritis" or whether they should be looked upon as incidental variations within the range of "normal".

This same question arises among gastroscopists today (6, 7, 8). There is much evidence to support the notion that small hemorrhagic lesions and so-called "pigment spots," regarded by many as signs of disease (2, 3, 4), are in reality artefacts due to the trauma of the gastroscope itself or to the suction applied to the wall by the stomach tube in making the preliminary gastric analyses. Ruffin (12), for example, has shown that the application of suction through a

*National Research Council Fellow in the Medical Sciences
From the New York Hospital and Departments of Medicine and Psychiatry of the Cornell University Medical College New York N.Y.
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Rehffuss tube in the process of obtaining gastric juice from the stomach sucked the mucosa against the holes in the tube and caused small submucosal and intramucosal hemorrhages. After several minutes these spots became black and appeared identical to the lesions described by many as "pigment spots."

Another change which has been considered of special significance in the diagnosis of "gastritis" is the size of the rugae in the stomach as they appear through a gastroscope. Ruffin (6) has shown that their

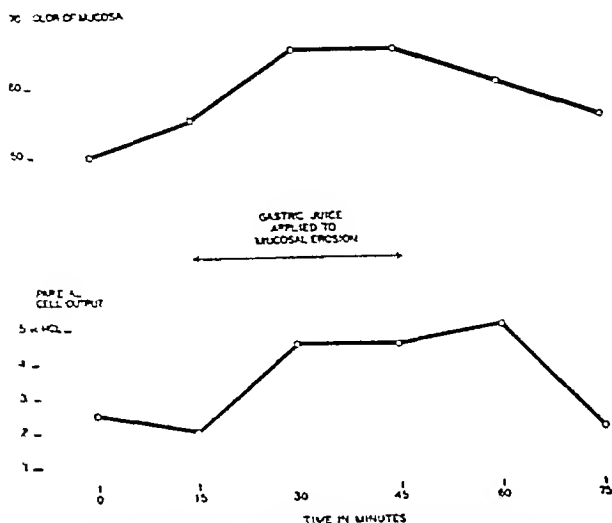


Fig 1 The acceleration of acid production following contact of gastric juice with an eroded mucosa

size may be a function of the quantity of air used in inflating the organ to provide an adequate view. With relatively large amounts of air, but not more than may be used during the course of ordinary gastroscopy, he found that the stomach lining could be flattened out entirely, so that it simulated the appearance of so-called atrophic gastritis. These observations we have confirmed in our subject as mentioned elsewhere (1).

"The Hyperfunctioning Stomach" and "Hypertrophic Gastritis" It has been pointed out in another publication that a hypersecreting stomach was always hyperaemic, turgid, engorged. This was true regardless of whether the accelerated secretion occurred in response to the stimulus of food, alcohol, histamine or to certain emotionally charged situations (10). When such a state of engorgement and hyperfunction was intense and prolonged the gastric mucosa assumed the characteristics of what is known to gastroscopists as "hypertrophic gastritis." The folds became thick, red and succulent. The slightest blow with the side of a glass rod, or stroking with a dry gauze resulted in the appearance of small hemorrhagic spots and erosions. Frequently these minute hemorrhages occurred spontaneously, following vigorous contractions of the stomach wall. The contractions themselves caused pain when they were of a sufficient magnitude, but not when the mucosa was pale and non-oedematous (11). When this hyperfunctioning, engorged condition of the stomach was prolonged in our subject he frequently complained of abdominal discomfort and pain.

Comment It is clear from above that many of the signs of "gastritis" may be encountered in the

normally functioning stomach or may be reproduced therein by minor traumata associated with instrumentation. To none of these changes discussed is the term "gastritis" altogether properly applied since there was no indication that actual infiltration of inflammatory cells occurred. The picture of "hypertrophic gastritis," for example, was found to be induced by vasomotor changes resulting in hyperaemia and congestion of the mucosa. These changes were often transitory, disappearing within an hour or two, a time too short for the subsidence of a true inflammatory process.

The fact that the congested mucosa was especially susceptible to injury, however, suggested that vascular engorgement might predispose to the development and persistence of erosions and changes secondary to inflammation. Furthermore, sustained hyperaemia of the gastric mucosa assumes added significance, since it was found to be accompanied by symptoms of abdominal discomfort and pain.

The Resting Gastric Mucosa In view of the special characteristics attributable to the mucosa during gastric hyperfunctioning, it seemed desirable to examine the behavior of the pallid resting gastric mucosa.

Method The mucosa was examined after a fast of 12 or more hours. In each case the stimuli were applied to folds of mucous membrane which ordinarily lay within the cavity of the stomach, but which were forced out through the stoma for the occasion by having the patient increase his intra-abdominal pressure. As noted elsewhere, this region of the stomach lining was of altogether healthy appearance. Many of the tests were also carried out on the collar of mucosa which always protruded through the stoma, and a few were made on remote parts of the stomach lining. In the latter group, observations of the membrane were made through a gastroscope.

After observing and in many instances, photographing the normal appearance of the mucous membrane, the stimulus was applied. The area was then observed continuously for one hour. Effects which persisted for a longer period were checked at intervals until they had disappeared.

The stomach was allowed to rest for from 2 days to



Fig 2 Normal mucosal folds (actual size)

a week between these particular experiments, and they were undertaken only when the gastric mucosa appeared relatively pale and inactive.

OBSERVATIONS

Sudden Mechanical Trauma When the mucosa was struck a sharp blow with the side of a glass rod, the area struck became blanched and depressed within one second. It remained so from 1-5 seconds, depending on the force of the blow. Following this there occurred

a slight transitory hyperaemia in the same region, which lasted for 3-10 seconds

Comment This effect has been observed before in dogs by others (13), who concluded that the trauma brought about a reflex contraction of the muscularis mucosae, which squeezed the blood from the mucosa for a few seconds

Continuous Mechanical Irritation. For 15 minutes an area of 2 sq cm was rubbed gently with the blunt end of a glass rod. Within 5 minutes the area had become slightly red and an obvious acceleration of mucus secretion had occurred. The mucus was thick and transparent and clung tenaciously to the wall of the stomach. A drop of Toepfer's solution allowed to fall on the region turned distinctly yellow, indicating that its pH was higher than 4.3

Negative Pressure. The stomach mucosa was sucked up against the hole in the side of a soft rubber catheter by the moderate negative pressure exerted by a 4 cm column of mercury for 1 minute. At that point a small, slightly-elevated purpuric spot, the size of the hole in the tube, appeared. After contact with the acid contents of the stomach for 15 minutes, the spot turned brown and then black. It thus had precisely the appearance of "pigment spots" in the stomach described by gastroscopists. The force of the negative pressure which caused this lesion was far less than that usually applied with a syringe in the course of a routine gastric aspiration which regularly precedes gastroscopy.

In order to measure the force ordinarily applied during gastric analysis the syringe was connected directly to a mercury U-tube manometer while a technician exerted the usual moderate tension on the plunger. The average negative pressure during 10 trials was 10 cm of mercury.

Abrasion of the Gastric Mucosa. The Protective Power of Mucus. Crystals of sodium chloride were sprinkled on the gastric mucosa and were then gently rubbed across its surface with the finger. Small linear hemorrhagic lines were produced where the sharp crystals had scratched the surface. A prompt accumulation of mucus was observed in the injured area. The appearance of the stomach lining elsewhere was not changed and no extra mucus secretion was observed except in the injured area. Here the acceleration of mucus secretion was estimated at 3 to 6 fold. No local oedema or other evidences of inflammation were observed.

The following morning, approximately 24 hours later, all but a few of the larger lesions had disappeared. Here one saw a scale of opaque precipitated mucus adhering firmly to the injured area. Its surface was spotted with blackened blood pigment.

This lesion had precisely the appearance of what is spoken of by some gastroscopists as superficial gastritis (2, 4).

48 hours after the lesion was inflicted, all evidence of abnormality had disappeared. This minor injury to the gastric mucosa was not accompanied by digestive complaints of any sort. The patient ate 2 hours after it was inflicted, and subsequently at his usual intervals. The stomach digested the food and emptied in the usual time.

Effects of Chemical Trauma. Acids and alkalis, drugs commonly taken by mouth, and condiments were applied directly to the stomach lining. Each substance

was rubbed very lightly on an area one centimeter square. Another area of similar size removed from the first site was selected as a control. This region was also rubbed lightly. Both were observed continuously for an hour. The reactions produced by irritating substances were classified in the following manner. A slight erythema within the limits of the test area was called a 1+ reaction. Moderate erythema within these limits was termed 2+. A 3+ was applied to erythema which extended beyond the one centimeter square, and 4+ was used to indicate an inflammatory reaction extensive enough to cause evidence of oedema of the mucous membrane. Below is a tabulation of the results obtained with the substances tested.

Drug	15 Min	½ Hr	1 Hr
Alcohol 20%	0	0	0
Alcohol 50%	0	0	0
Alcohol 100%	0	0	0
Histamine 1%	0	0	0
Acetyl salicylic acid (Powd pill)	0	0	0
Sulfanilamide	0	0	0
Sulfapyridine	+	++	++
Sulfathiazole	0	0	0
Sulfaguanidine	0	0	0
Sulfadiazine	0	0	0
Ammonium chloride	0	0	0
Digitalis	0	0	0
Quinidine	0	0	0
Glucose 50%	0	0	0
Mustard (1:30 susp in water)	+	++	++
Hydrochloric acid 1 N	+	++	++
Sodium hydroxide 0.1 N	+	++	++

These same agents were similarly applied to an area on the volar surface of the forearm. The 50% and 100% alcohol produced moderate local erythema. The mustard, hydrochloric acid, and sodium hydroxide produced swelling, tenderness and vesiculation in addition to erythema. These effects were far more intense than the designated 4+ reaction.

Comment. The failure of strong irritants and corrosive agents to cause more than a slight-to-moderate erythema in the gastric mucosa, while they caused marked reaction with destruction of tissue when applied in similar concentration to the skin, is striking. It indicates that the cells lining the stomach are endowed with some special protection against chemical injury. The neighboring esophagus is not so well protected. Irritants brought into contact with the latter are well known to cause inflammation with pain and occasionally stricture.

Presumably the special protection is afforded by the thick layer of tenacious mucus which is adherent everywhere to the stomach lining and which is elaborated in increasing amounts in response to physical and chemical stimuli, thus protecting the membrane from significant injury.

Properties of Mucus When a drop of Toepfer's solution was allowed to fall on the exposed collar of the mucous membrane or even on the stomach wall within the stoma, it failed to turn red until it came in contact with an accumulated pool of gastric juice. When this test was made, a specimen had just been poured out containing 65 units of free acid, and all parts of the stomach wall including the exposed collar were moist with that secretion. A drop of phenolphthalein was applied in like manner and this, too failed to be-



Fig 3 Engorgement of mucosa accompanying emotional conflict (same scale)

come red. Thus it was concluded that the pH of the surface of the stomach wall lay between 4 and 7, although it enclosed a juice of less than pH 2.

Thus the layer of mucus which clings everywhere to the stomach lining is sufficiently alkaline to maintain the surface of the gastric mucosa in a relatively neutral environment, despite the high concentration of acid in the gastric juice which it encloses.

In addition to its capacity to neutralize, mucus displayed another characteristic which makes it an effective insulator for the cells lining the stomach. This was demonstrated in the following way:

1 N hydrochloric acid was allowed to fall upon the gastric mucosa at the rate of 12 drops a minute. At once the acceleration of the output of mucus was apparent, and the mucus which the drops of acid touched became grey and opaque. This layer was pulled away with considerable difficulty from a small area. The grey, membranous flakes thus obtained were found to be relatively insoluble in gastric juice, in 0.1 N hydrochloric acid and even in 1.0 N hydrochloric acid.

To test this protective power, an attempt was made to deprive a part of the gastric mucosa of its mucus covering and then to subject it to irritating stimuli.

Production of Gastritis After Attempts to Remove Covering of Mucus 1.0 N hydrochloric acid was allowed to fall upon the exposed gastric mucosa drop by drop as outlined above. Within 2 minutes a thick layer of greyish opaque mucus had appeared over the area exposed to the acid. The rate of application of the drops was increased from 12 to 20 a minute, while the accumulated mucus was sucked away through a pipette. Within 5 minutes the mucosa beneath became moderately reddened and oedematous. The 1-30 mustard suspension was then applied and its effect observed. Within 5 minutes the redness and oedema was further accentuated and very minute bleeding points became evident as pin-point black specks on the mucosa where drops of hemoglobin had been altered by the hydrochloric acid present.

Mechanical trauma were also applied to the gastric mucosa in its state of induced inflammation. A sharp blow with a glass rod which formerly resulted in a transitory blanching and subsequent reactive hyperaemia now induced minute bleeding points. Rubbing with the blunt end of a glass rod also caused hemorrhage, and as pointed out in another publication (11) these mechanical stimuli applied to such an area caused pain.

Acceleration of Acid Output by Contact of Gastric Juice with Minute Erosions Two of the small hemorrhagic lesions described in the preceding paragraph were kept in contact with gastric juice with a titratable total acid of 90 for $\frac{1}{2}$ hour. Mucus accumulated rapidly in the region, but it was removed at frequent intervals by suction through a small glass tube, and the acid gastric juice was then reapplied to the bare mucosa. A sharp acceleration of acid secretion and concomitant hyperaemia of the whole stomach mucosa occurred and persisted for $\frac{1}{2}$ an hour after the submersion of the hemorrhagic lesions was discontinued (Fig 1).

Comment In this phenomenon may lie an explanation of the persistent hyperacidity regularly encountered in persons suffering from "gastritis" and peptic ulcer. The fact that the base of the ulcerated lesions which is constantly bathed in acid gastric juice effects a stimulation of acid secretion indicates that afferent impulses subserve this reflex without sensation resulting. It is likely, however, that pain would follow an adequate chemical stimulus (14).

The Effect of Gastric Juice on an Area of Mucosa Lacking in Mucus The most peripheral edge of the collar of mucosa which lay exposed on the abdominal wall lacked adequate protection owing to defective formation of mucus in this region. A small erosion which occurred on this peripheral edge was exposed continuously to the digestive action of gastric juice for 4 days. During the first 24 hours the denuded surface increased in size. It bled intermittently. At the end of 4 days it exhibited the typical punch-out appearance of a chronic peptic ulcer with well-defined edges and a granulating base. It measured approximately 4 mm in diameter, 1 mm in depth and was growing rapidly (Fig 2). Traction or pressure on

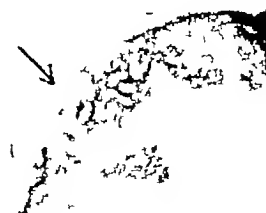


Fig 4 Mucosal erosion (same scale)

this lesion resulted in pain of a dull, gnawing character, which was localized in the region of the lesion itself. Throughout the 4 day period the whole mucosa was relatively engorged, and the rate of acid secretion was significantly elevated.

At the end of 4 days because of the hazard to the subject it was felt that the experiment could not be allowed to continue.

The ulcer and surrounding area were covered with a protective petrolatum dressing. Within 3 days com-

plete healing had taken place, leaving no trace of the lesion behind

DISCUSSION

It is clear that gastric juice is quite capable of attacking and digesting the mucous membrane of the stomach. It does not do so under normal circumstances because it does not gain access to it. Neither does it do so under irritating and corrosive substances taken as articles of diet, because the lining of the stomach is normally covered by an efficient insulation in the form



Fig 5 Punched-out ulcer resulting from prolonged contact of gastric juice with an area of mucosa inadequately protected by mucus (same scale)

of a protective covering of tenacious, viscous, alkaline mucus. The latter combines with the acid in its immediate vicinity and thus maintains the cells of the gastric mucosa in a relatively neutral chemical environment. It effectively diverts the force of any mechanical trauma or abrasive which may brush by, by presenting a slimy, mucinous surface. Finally, in the presence of strong acid it precipitates and forms a relatively insoluble membranous shell over the delicate mucosal cells. Once the vast protective powers of mucus are overcome, however, and the digestive juices have attacked and eroded the surface of the mucous membrane, a vicious cycle is set up since the acid gastric juice in contact with a denuded region induces further acid secretion.

Chronic ulceration then is the resultant of the interplay of forces protective and destructive. If a minor erosion can be effectively covered with mucus and the hyperfunction of the stomach subsides spontaneously or can be made to subside by the ingestion of fat or the administration of drugs, healing takes place quickly and uneventfully. If, on the other hand, hyperaemia and hypersecretion are sustained by a stimulus which overwhelms the inhibitory influence of fat or drugs, the susceptibility of the mucosa to injury is enhanced and tissue damage proceeds unchecked, resulting in ulceration.

SUMMARY

The healthy gastric mucosa varied in appearance within a wide range. When the rate of acid production

by the parietal cells was relatively slow the mucosa was always comparatively pale and in this state relatively resistant to injury unless the continuity of its protective covering mucus was interrupted.

Accelerated acid production and motor activity were always accompanied by hyperaemia and engorgement of the mucosa. When vascular engorgement was prolonged the rugae became intensely red, thick and turgid presenting the picture of what has been called "hypertrophic gastritis." In this state the mucosa was unusually fragile, haemorrhages and small erosions resulting from even the most minor traumata. Lowering of the pain threshold occurred and symptoms were often associated with this condition. Thus the difference between hyperfunction in the stomach and "hypertrophic gastritis" was seen to be mainly one of degree. Continued exposure of a small erosion to the digestive action of gastric juice for 4 days resulted in a peptic ulcer.

CONCLUSIONS

1 Undue and prolonged acceleration of acid secretion in the stomach, however provoked, resulted in hyperaemia and engorgement of the mucous membrane resembling hypertrophic gastritis.

2 The mucosa in this state was unusually susceptible to injury, and even the most trifling traumata resulted in hemorrhages and small erosions.

3 Ordinarily the mucosa was protected from injury by an effective coating of mucus. Loss of this protection in the face of minor traumata led to oedema, inflammatory changes, erosions and hemorrhages.

4 Contact of acid gastric juice with a denuded surface induced further hyperaemia and acceleration of acid secretion.

5 Prolonged contact of acid gastric juice with a minor erosion resulted in the formation of a peptic ulcer.



Fig 6 Drawing of ulcer (enlarged five times)

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Peptic Ulcer in the Aged; a Clinical and Post-Mortem Study

By

JACOB MEYER, M D

and

OTTO SAPHIR, M D

CHICAGO ILLINOIS

It is generally believed that peptic ulcer in the aged is uncommon. Recently however Mulsow (1) reviewed the literature on peptic ulcer in the aged, and stated that 10.5% of 4,079 patients were above the age of 60. The concept generally held is that when peptic ulcer occurs in the aged, it is chronic, of many years duration, and that the hemorrhage and perforation which occur are complications of an old peptic ulcer.

This study is a report not only of the occurrence of chronic peptic ulcer in the aged, but also of the occurrence of recent acute peptic ulcers in the sixth and later decades of life. Such acute ulcers constitute an unexpected and often unrecognized complication of many diseases and are often the cause of death because of hemorrhage or perforation. Occasionally these acute ulcers became chronic.

This communication comprises the study of 16 patients. The youngest was 60 years old, the oldest, 83. Six were between 60 and 69 years old, seven between 70 and 79, and three over 80 years. There were 12 males and four females. Two patients were negroes.

The clinical diagnosis of peptic ulcer was made in five patients. In two additional patients this diagnosis was made at operation in one patient in whom the diagnosis of carcinoma of the stomach had been made, and in another with the pre-operative diagnosis of ileus. The main clinical diagnosis of the other nine patients in whom the peptic ulcer was not recognized clinically were carcinoma—of the bronchus, of the prostate of the sigmoid colon, and of the stomach, or colon respectively, cholecystitis with cholelithiasis, intestinal obstruction in two perforated viscus and cor pulmonale.

The clinical findings in the five patients in whom the ulcer was correctly diagnosed, were quite characteristic and corresponded with the findings in patients with peptic ulcer in the younger age group. The ages of these patients were 60, 62, 74, 79 and 81 respectively. Post-mortem examination disclosed that one patient had a penetrating gastric ulcer, another a recent gastric and duodenal ulcer, the third had two duodenal and two gastric ulcers, one of which had perforated and produced a diffuse peritonitis, the fourth had a penetrating ulcer in the duodenum with

erosion of the pancreoduodenal artery and fatal hemorrhage. The fifth patient also died of hemorrhage produced by erosion of the left gastric artery by a penetrating peptic ulcer.

The following two short clinical abstracts may indicate that it is possible to recognize the onset of acute peptic ulcer in patients who are 60 years old or older, and who never have had a previous story of epigastric distress.

A 61 year-old white female developed epigastric and precordial distress. There was no complaint of discomfort in her earlier life. X-ray examination revealed a gastric ulcer on the lesser curvature. One year later she had a severe hematemesis, from which she recovered on simple medical management. Five years later she again experienced a severe hematemesis, the red blood corpuscle count being 1,300,000. She improved on medical treatment. An X-ray examination at this time showed a defect on the lesser curvature, and she was referred to the out-patient department.

Another patient, a male at the age of 75 developed epigastric distress typical of ulcer. An X-ray examination revealed a duodenal defect. He was treated in the out-patient department for a duodenal ulcer and for diabetes. Eventually he developed a carbuncle of the neck, was admitted to the hospital, and died two days later. The autopsy disclosed a duodenal ulcer with erosion of the pancreoduodenal artery.

These two patients illustrate the fact that an acute ulcer may occur in people past sixty years of age, and that the ulcer may be recognized and treated as such. Mulsow has emphasized that gastric syndromes in the aged generally raise suspicions of carcinoma, and that the possibility of peptic ulcer is not even entertained. His patients had chronic ulcer of many years' duration.

Among clinicians the concept prevails that the occurrence of an ulcer syndrome in the aged is due to recurrence of symptoms of an old ulcer. The point is generally made that aged patients generally forget the history of previous gastric symptoms. Such statements are undoubtedly correct in some instances but it has been our experience to find evidence of acute gastric and duodenal ulcers together with evidence of healed or chronic gastric and duodenal ulcers. Two cases may serve to illustrate such an occurrence.

*From the Departments of Internal Medicine and Pathology of Michael Reese Hospital Chicago, Illinois.

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A 71 year-old female had been treated for one year for duodenal ulcer and showed evidence of improvement. Four days previous to hospital admission, she developed severe cramps, nausea and vomiting. The diagnosis now was intestinal obstruction. An autopsy disclosed an acute perforated gastric ulcer and a healed duodenal ulcer. Another patient, a 74 year-old female, gave a history of ulcer of many years' duration. One week previous to admission she developed severe abdominal pain. The diagnosis was perforated duodenal ulcer. At operation a perforated duodenal ulcer was sutured. The patient died four days later. The autopsy disclosed two old chronic "kissing" duodenal ulcers, one of which had perforated. The surgeon had sewn the perforated duodenal ulcer but had overlooked an acute perforated gastric ulcer. It would seem that the last painful attack for which the patient was admitted, was due to the perforated gastric ulcer.

In connection with the subject of age and the onset of gastric symptoms of ulcer, Eusterman and Balfour (2) may be quoted. They compiled a table indicating the age of patients at the onset of symptoms, and the age at time of operation. Among the age group 60-70, they noted eight patients with duodenal and fifteen with gastric ulcer.

In striking contrast to these clinically outspoken, acute gastric and duodenal ulcers in the aged, we have observed acute peptic ulcers at the autopsy table as an unexpected and unrecognized complication. In the majority of these patients there were few or no gastro-intestinal symptoms to direct the attention of the clinician to these complications. As stated before, these acute peptic ulcers have been observed following acute febrile disease, operation for gall stones, resection for carcinoma of the stomach, carcinoma of the prostate, prostatic resection, carcinoma of the lung, congestive heart failure and coronary disease. Autopsy revealed, in addition to the primary disease, acute peptic ulcer, single or multiple, gastric or duodenal, which were bleeding or had perforated into the peritoneal cavity.

It is important to emphasize that the occurrence of these acute ulcers is most often asymptomatic with reference to the gastro-intestinal tract. Blood in the stools may lead the clinician to an early diagnosis. The symptoms suggesting gastric hemorrhage or shock in patients post-operatively are generally attributed to the operative procedure. Symptoms, when present, are those of acute abdominal pain, nausea, vomiting and later abdominal distention. In general, the diagnosis most commonly made is intestinal obstruction. Interesting is the fact that in the patients with acute perforation, the abdomen was not rigid.

The association of coronary disease and peptic ulcer is of particular interest in view of the similarity in the clinical syndrome, particularly in patients with recent perforations. A patient with coronary disease may have an ulcer syndrome, with or without a peptic ulcer and vice versa, or a patient may have both coronary disease and peptic ulcer. In our series post-mortem examinations disclosed nine patients with coronary sclerosis or thrombosis associated with peptic ulcer. In only four of these patients was the ulcer diagnosed. Coronary artery disease was suspected and

diagnosed in three instances. The following table I is significant in this respect.

TABLE I

Case No	Autopsy Findings in Addition to Severe Coronary Artery Sclerosis	Relevant Diagnosis From History and Symptoms
1	Acute gastric ulcers (2)	No symptoms of ulcer or coronary
3	Gall stones operation 7 acute gastric ulcers	Symptoms of both gall bladder disease and angina pectoris No ulcer symptoms recognized
4	Acute gastric and duodenal ulcers Dilated esophageal veins	Ulcer suspected Coronary sclerosis
6	Chronic duodenal ulcer Healed infarct of myocardium	Carcinoma of prostate
7	Perforated duodenal ulcer	Coronary suspect. Urinary bladder infection
8	Acute duodenal ulcer with perforation	No diagnosis except symptoms of intestinal obstruction
11	Chronic gastric ulcer with erosion of gastric artery	Ulcer diagnosed
12	Acute perforated gastric ulcer Healed duodenal ulcer	Ulcer diagnosed
14	Chronic duodenal ulcer with erosion of pancreoduodenal artery	Ulcer diagnosed

Not only is the recognition of both conditions in the aged difficult, but the decision as to the best method of treatment in such instances is even more difficult. With the present increased interest in old age and its problems, there is the possibility that this disease may be recognized sufficiently early and some of these patients saved.

The etiology of acute ulcer in the aged offers much for speculation. We direct attention to the well known observation of diminution in hydrochloric acid and pepsin in the aged. In this series one patient, who had an acute perforated ulcer, had a free acidity of 11. We doubt that the degree of acidity or accumulation thereof plays an important role in the genesis of ulcer in the aged. It seems more likely that as a result of increasing sclerosis of the larger and smallest arteries, local necrosis occurs which favors the development of an ulcer. It is also conceivable that during operation, or post-operatively, changes in the circulation, such as the fall in arterial blood pressure, etc., may play a role in the causation of these ulcers. Such acute ulcers occur within a short period (four to seven days) after operation and hemorrhage and perforation occur within this period after an operation. It is known that Vitamin C is diminished in the aged. It is possible that the lack of this substance in the aged may be a predisposing factor, not only to the genesis of ulcer, but also to the rapidity of development of the ulcer and its progression to perforation.

Seven of these patients with peptic ulcers had Wangenstein tubes inserted for various lengths of time before they died. In one of the patients, considered to have cholelithiasis, in whom at autopsy seven small gastric ulcers were found, the tube had been present for about 52½ hours. Some of the recent ulcers were situated in the posterior wall of the stomach at a short distance from the cardiac end. One of the ulcers was oblong, its cross diameter being about equal to the diameter of a Wangenstein tube. Another patient, diagnosed clinically as having carcinoma of the sigmoid colon, had a Levine tube inserted for eight days prior to death. At autopsy two ulcers were

present in the duodenum. A third patient, in whom the clinical diagnosis was ileus, had had a Wangenstein tube for a period of six and one-half days before death. At autopsy a perforated gastric ulcer was found. Thus, the question must be considered as to whether or not the pressure of a Wangenstein or Levine tube upon the mucosa of the stomach may constitute a further factor in the causation of some of these peptic ulcers.

At autopsy the various ulcers grossly were similar in their appearance and location to those seen in the younger age group. Histologically there were outstanding changes in the smaller arteries throughout the stomach wall, particularly pronounced in the region of the ulcers. These changes were typically arteriosclerotic with marked intimal thickening and reduction of the lumen. Though it is realized that similar changes are found at the bases of ulcer taken from stomachs of patients in all age groups, the

vessel changes encountered in the older age group seemed definitely more severe.

SUMMARY

While it is generally accepted that chronic peptic ulcer occurs in the aged and that such patients die from the complication of hemorrhage and perforation of a chronic ulcer, this study directs attention to the occurrence of acute peptic ulcers in the aged. Such acute ulcers may become chronic, but more often they result in acute hemorrhage and perforation causing the death of the patient. Such acute ulcers may be primary, or secondary in association with acute febrile disease, gall bladder disease, operative procedure, or cardiac failure. Factors which may be contributory to the genesis of peptic ulcers are discussed.

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Unusual Vascular Diseases Within the Abdomen

By

STOCKTON KIMBALL, M.D., MORTON H. LIPSITZ, M.D.

and

KORNEL TERPLAN, M.D.
BUFFALO, NEW YORK

WE are presenting a summary of some of the pathological and clinical manifestations of diseases of the large and small intra-abdominal vessels which may cause acute or chronic disease of the intra-abdominal organs. This report is based on a series of cases observed at the Buffalo General Hospital over the past ten years. Several of these are unusual and of particular interest. We are omitting consideration of heart disease which mimics abdominal disorders. Our cases are summarized in Table I.

TABLE I
Occlusion

Aorta (Thromb-emboli)	2	
Thrombosis	1	
Mesenteric Vessels (Artery or Vein)	15	
Splenic — I. Artery	3	
II. Vein	1	
Left Gastric Artery	1	
Portal Vein	2	
Inferior Vena Cava	1	
Renal Veins	1	
Iliac Veins (carcinomatous invasion)	1	
Multiple	1	28

Aneurysm

Abdominal Aorta		
1. Luteal	1	
2. Atherosclerotic (ruptured 2)	3	
3. Dissecting	1	
Splenic Artery—ruptured	1	6

Peri-arteritis nodosa

1 PERI ARTERITIS NODOSA	4	4
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Malignant hypertension

(Ulcerating necrotizing enteritis with volvulus)	1	1
		40

The vessels involved in these cases were

1. Aorta
2. Branches of Aorta
3. Small Arteries and Arterioles
4. Portal System
5. Systemic Veins and Tributaries

PATHOLOGY

Degenerative processes and inflammation were the two major pathological conditions found in the arterial cases. The degenerative process was atherosclerosis of either the larger or small arteries, with a superimposed medial necrosis in one case of malignant nephrosclerosis. The inflammatory process was a luteal arteritis in one case, and an arteritis of the small arteries in four cases of periarteritis nodosa.

These pathological processes were complicated by aneurysm formation, necrosis, hemorrhage or thrombosis in arteries of all sizes. We have included also instances of thrombembolism of arteries of any size due to the lodging of emboli originating in the heart or the walls of the aorta.

The pathology in the veins was in all instances one of thrombosis secondary to some form of venous obstruction which caused a slowing of the rate of blood flow. The causes of venous obstruction included pressure by metastatic nodes, direct involvement of the veins themselves by carcinoma, splenic infarct and primary calcific thrombosis.

SYMPTOMS

Vascular disease, per se, is symptomless. The symptoms in our cases were the result of the complications of vascular disease—aneurysm formation

necrosis, hemorrhage, vascular occlusion by embolus or thrombus

The mechanism of symptom production was as follows

1 Aneurysm—Pressure produces pain Perforation produces hemorrhage Thrombosis may produce vascular occlusion directly or by forming emboli

2 Hemorrhage—Causes further pressure symptoms Produces picture of internal hemorrhage, blood loss, shock

3 Vascular Occlusion (Arteries or Veins)—May be gradual or sudden Tissues are deprived of blood supply, tissues atrophy, tissues die

Vascular occlusion is the commonest cause of symptoms due to vascular disease Gradual occlusion results from vascular narrowing or from occlusion of smaller branches This leads to scarring and atrophy of involved organs Instances of "Abdominal Angina" in the literature have been attributed to this cause Gradual occlusion may mimic chronic cholecystitis, cholelithiasis, peptic ulcer, malignant tumor, colitis, chronic appendicitis or pelvic disease Sudden occlusion produces infarction, necrosis, perforation, peritonitis and hemorrhage Sudden occlusion leads to a picture resembling an "acute surgical abdomen" and may imitate such conditions as acute cholecystitis, gall stone colic, acute pancreatitis, perforated ulcer, intestinal obstruction, strangulated hernia, appendicitis, diverticulitis or acute pelvic disease One of our cases manifested painless rectal hemorrhage and constipation mimicking carcinoma of the colon

It is important to keep in mind that any vessel, in any position, and of any size may be involved by any of the pathological processes and their complications which have been mentioned The symptoms produced by vascular disease vary according to the type, position and size of the vessel involved, and the nature, extent and speed of the involvement The symptoms essentially are the result of pressure, blood loss, and vascular occlusion

ILLUSTRATIVE CASES

Aorta In eight of our cases the abdominal aorta was chiefly affected The complications present were aneurysm formation, hemorrhage and occlusion Of the five cases of aneurysm, one was a syphilitic aneurysm complicated by thrombosis, and four were atherosclerotic Two of the atherosclerotic aneurysms had ruptured, one had not ruptured and was symptomless, and one was a dissecting aneurysm with rupture The two cases of atherosclerotic aneurysm with rupture were unusual clinically One simulated a perineal abscess, the other a strangulated inguinal hernia

Case 1 Ruptured Atherosclerotic Abdominal Aneurysm Mimicking Perineal Abscess Female, age 78, admitted 1-21-40, died 1-28-40

CC Four weeks previously she had "recovered" on sulfapyridine from a pneumococcus, Type IV, pneumonia One week before admission she began to complain of pain in the precordium and lower right abdomen The pain became more severe, more localized in the right lower quadrant, and before her death, in the right flank On admission the pain was considered to be "out of proportion for appendicitis" It resisted morphine On 1-24-41 there was noted the "suggestion of a diffuse mass anteriorly which may be extra-peritoneal on the anterior surface of the kidney or in the ascending colon or cecum" The blood pressure was 168/80, and the temperature was normal

The blood count was as follows Hemoglobin 76%, R B C 4,000,000, W B C 2800 to 60,000, with a definite left shift The blood culture showed 10 colonies of pneumococcus, Type IV The stool was twice negative for blood, and the urine showed a trace of albumin, 2-3 red blood cells, 10-15 white blood cells per h p f X-ray of the chest demonstrated clear lung fields, with the right costo-phrenic angle obliterated A flat film of the abdomen showed no evidence of free air or dilated small bowel The temperature showed a few spikes The patient was given sulfapyridine with no results She became gradually weaker and expired The clinical impression was perinephritic abscess on the right side

Autopsy Findings

1 Atherosclerotic aneurysm of the abdominal aorta, with recent rupture and huge perirenal hematoma

2 Generalized anemia

3 Chronic, in part organized, bronchopneumonia and atelectasis in left lower lobe

Case 2 Ruptured Atherosclerotic Aneurysm Imitating Strangulated Inguinal Hernia Male, age 62, admitted 5-1-37, died 5-5-37

CC Pain started in the lumbar region on 4-29-37 and grew progressively worse until patient went into shock He gradually rallied, and then on 4-30-37 he complained of pain to the left of the epigastrium which slowly travelled down to the left inguinal region His abdomen became distended and all food was vomited He was hospitalized on 5-1-37 because of suspected strangulated hernia and bowel obstruction

PE Patient in shock The heart and chest were negative Temperature 100°, pulse 100, respirations 20, blood pressure 94/60 The abdomen was markedly distended with dullness to flatness in the flanks, and was tender all over A sausage-shaped, firm mass was felt in the left inguinal region—tender to palpation with negative to cough impulse There was no audible peristalsis Genitalia were negative The reflexes were normal

Course The patient was believed to have an incarcerated left inguinal hernia and was operated upon at once by Dr J S Regan On incising, the mass proved to be a blood clot, and on opening the abdominal cavity there was free blood associated with an abdominal aneurysm The patient was returned to his room after closure of the wound and died several hours later

Autopsy Findings Huge ruptured saccular atherosclerotic aneurysm of the abdominal aorta, with hemorrhage into the retro-peritoneum and peritoneal cavity

Case 3 The Third Case of Atherosclerotic Aneurysm Was Operated Upon for True Strangulated Femoral Hernia Male, age 64 History of angina pectoris past two years, more frequent of late Admitted and operated for resection of ileum strangulated in femoral canal Stormy post-operative course, followed by sudden death 3 days after admission

Autopsy Findings

1 Ileostomy after resection of ileum

2 Extensive generalized atherosclerosis coronary sclerosis with extensive scarring of myocardium, calcific process involving mitral and aortic valves

3 Abdominal aortic aneurysm—lemon size—just above the bifurcation

Case 4 Typical Dissecting Aneurysm of Aorta Male, age 52, admitted 5-15-37, died 5-21-37

CC Two days previous to admission, patient had sudden, prostrating, stabbing pain, starting in the back and radiating over the precordium to both shoulders, more to the left, associated with vomiting and much gastric distress There was a history of hypertension, dyspnea and palpitation on exertion with moderate ankle edema in the past two years

PE Evidence of shock T 100° (R), P 120, R 20, BP 80/50 She was pale and drowsy The heart was

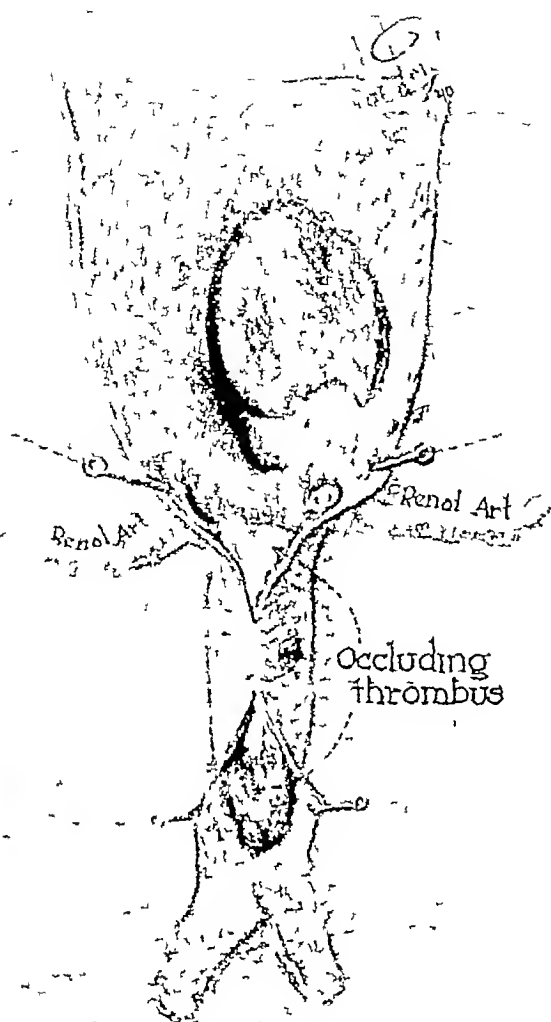


Fig 1 Case 5 Syphilitic aneurysm of abdominal aorta with marked parietal thrombosis. Complete thrombotic occlusion of abdominal aorta below level of renal arteries, and complete thrombotic occlusion of right renal artery.

moderately enlarged, rapid, regular, with fair tones and no murmurs. The lungs, abdomen and extremities were negative.

Blood Count Hemoglobin 60%, RBC 3,800,000, WBC 20,400, Polys 75%. Serology negative.

Urine Albumin 1-plus, few wbc

ECG T₁, T₂, T₃ negative. Elevated R-T. Inverted QRS.

Course On the 3rd day he suffered another severe knife-like pain in the lower precordium which seemed to come from the back and radiated to the shoulders. He went into shock, grew steadily worse, and expired two days later.

Autopsy Findings

1 Considerable atheromatosis of entire aorta

2 Dissecting aneurysm starting in the arch at the site of the ductus arteriosus and opening into the iliac vessels, with marked fatal hemorrhage into the pleural cavity on left, causing complete atelectasis of the left lung and hemorrhage of mediastinum

3 Hypertensive type of heart with dilated, hypertrophied left ventricle

Case 5 The following case of luetic aortitis of the abdominal aorta with aneurysm and complete thrombosis of the abdominal aorta is significant because of the infrequency of syphilis of the abdominal aorta. Male, age 64, admitted 10-14-40, died 10-16-40

CC The patient was an old tabo-paretic who had been treated with malaria and adequate intravenous and intramuscular therapy. He was feeling well. He went into the bathroom to defecate and on attempting to rise, found he was unable to move. There was no pain but there was an entire loss of sensation and motor power in both lower extremities. He was hospitalized immediately.

P.E T 103° (R), P 100, R 28, BP 90/70. Pupils normal, chest clear, heart slightly enlarged, abdomen distended, anal sphincter relaxed and incompetent. Examination of extremities showed complete paralysis, with several superficial areas of gangrene. The feet were cold and pulseless. There were no pulsations even in the femorals. All deep reflexes were absent.

Blood Count Hemoglobin 86%, RBC 4,300,000, WBC 22,000, Polys 81%

Urea Nitrogen 57 mg per 100 cc

Course Progressively downhill, with fall in temperature to 98°, expired despite transfusions and fluids intravenously.

Autopsy Findings (Fig 1)

1 Diffuse meso-aortitis syphilitica of thoracic and abdominal aorta with sacular aneurysm and marked parietal thrombosis within the abdominal portion

2 Recent complete thrombotic occlusion of abdominal aorta below level of renal arteries, and of right renal artery

3 Severe hemorrhages in iliolumbar muscles. Early gangrene of lower extremities

4 Recent bronchopneumonia of right lower lobe

Case 6 Severe Atherosclerosis of the Abdominal Aorta. Autopsy showed parietal thrombosis leading to occlusion of the mesenteric arteries by direct extension. This will be discussed with the group of cases of mesenteric occlusion. It is mentioned here to exemplify parietal thrombosis of the aorta on the basis of atherosclerosis to compare with the parietal thrombosis in Case 5 developing on the basis of syphilitic aortitis.

Cases 7 and 8 Embolism of the Abdominal Aorta in Patients with Mitral Stenosis and Auricular Fibrillation. Both cases showed an acute onset of severe abdominal pain: the first, in the lower abdomen slightly to the left of the midline, gradually extending straight up the midline to the ribs, referred to both shoulders and associated with emesis; the second, in the pelvis, with a sensation comparable to the beginning of menses and accompanied by a bowel movement. Both resulted in complete paralysis and numbness, coldness, whiteness, areas of discoloration and absence of pulsation in both lower extremities, even in the femorals. The symptoms closely resembled those in Case 5.

Case 7 A male, aged 48, died four days after the attack and showed at autopsy mitral stenosis, thrombembolism of the abdominal aorta, gangrene of both legs, gangrenous infarction of 30 cm of small intestine, and anemia infarction of both kidneys.

Case 8, a female, aged 44, who showed symptoms and physical findings in the heart and extremities just like those in Case 7, did not die, but recovered after 3 months with full use of both legs. It seems reasonable to assume that she represents an instance of saddle embolus of the abdominal aorta with recovery.

This group of 8 cases illustrates how either atherosclerosis of the abdominal aorta or luetic aortitis may lead to aneurysm formation, hemorrhage or thrombosis and shows how similar results may also follow embolism to the abdominal aorta from the heart. All

of these complications may be followed by dramatic and often bizarre symptoms and signs so that the possibility of vascular disease must always be kept in mind during the diagnosis of the acute abdomen

MAJOR BRANCHES OF AORTA

Among our cases are twenty of involvement of the major branches of the abdominal aorta, three-quarters of these being mesenteric occlusion. Occlusion of the iliac vessels has not been included in this series because the symptoms are primarily in the lower extremities. It must always be remembered that in some of these cases intra-abdominal embolectomy may save a life.

The left gastric artery was involved in one case.

Case 9 *Thrombosis and Rupture Left Gastric Artery* Male, age 69, admitted 3-4-38, died 3-10-38.

CC On 3-2-38 there was an acute onset of upper abdominal pain, sharp and crampy, associated with nausea. He had a small liquid stool next morning, pain continued, colicky, and with increasing frequency. There was a history of bronchial asthma since 1901. He has had attacks of precordial pain associated with dyspnea, palpitation and edema of ankles. There were no previous GI symptoms.

PE T 100, P 120, R 32, B P 182/94

Chest Emphysematous, coarse inspiratory rales at bases.

Heart Enlarged, tachycardia, tones fair, no murmurs, vessels sclerotic.

Abdomen Distended, marked full appearance of R U Q, no visible peristalsis, tenderness throughout, especially in mid-epigastrium, tympanic note, peristalsis feebly heard throughout, muscular rigidity throughout, especially in R U Q, no rebound tenderness.

Extremities No edema.

Blood Count Hemoglobin 84%, RBC 4,350,000, WBC 14,300. Bands 12, Filaments 68, Van den Bergh 0.55 mg %.

X-ray—GI Tract Some interference with onward passage of barium in region of hepatic flexure. Considerable distension of colon and stomach with gas.

Heart Moderately enlarged to left.

Course Because of possible intestinal obstruction, abdomen was explored. Free blood in peritoneal cavity. Transverse colon markedly distended. Cecostomy performed. Patient failed after surgery and died on 4th post-operative day with signs of terminal bronchopneumonia.

Autopsy Findings

1 Hypertension

2 Marked atheromatosis of left gastric artery with diffuse thrombosis and minute rupture. Moderate intra-abdominal hemorrhage in process of organization.

3 Status following cecostomy

4 Confluent recent bronchopneumonia of both lungs

The splenic artery was involved in three cases.

Case 10 *Ruptured Aneurysm of the Splenic Artery with Massive Hemorrhage Into the Lesser Sac* (Previously reported by Machemer and Fuge (1)). Female, age 30, admitted and died 1-15-38.

CC On 1-13-38 there was onset of indefinite, burning, epigastric pain and nausea. The next day pain was more severe and located in R U Q, with radiation to right shoulder blade and right costal margin. The following day the pain gradually decreased, replaced by sharp, crampy, L L Q pain and shock.

PE Shock. Blood pressure 78/62. There was exquisite tenderness and spasm in both lower quadrants and in both fornices.

Blood Count Hemoglobin 48%, RBC 2,280,000, WBC 7,500.

Autopsy Findings (Fig 2)

1 Chronic rheumatic endocarditis of mitral and aortic valves

2 Ruptured aneurysm of splenic artery with massive hemorrhage into the peritoneal cavity

3 Old infarct of left kidney

4 Marked generalized anemia

Cases 11 and 12 were two remarkable and very similar cases of occlusion of the splenic artery which well illustrate the widespread effects of vascular occlusion.

Case 11 *Occlusion of the Splenic Artery* (previously reported by Milch and Masotti (2)). A white male, aged 53, with a history of occlusive peripheral arterial disease of both extremities of 1½ years duration. He suddenly developed excruciating abdominal pain and collapsed. Eight hours later he vomited coffee-ground material and developed bloody diarrhea, marked tenderness in the epigastrium and left flank. There was no spasm or distension.

Blood count showed WBC 35,000 and Polys 93%. The ECG showed evidences of old infarction. Death ensued 12 days after onset of abdominal pain.

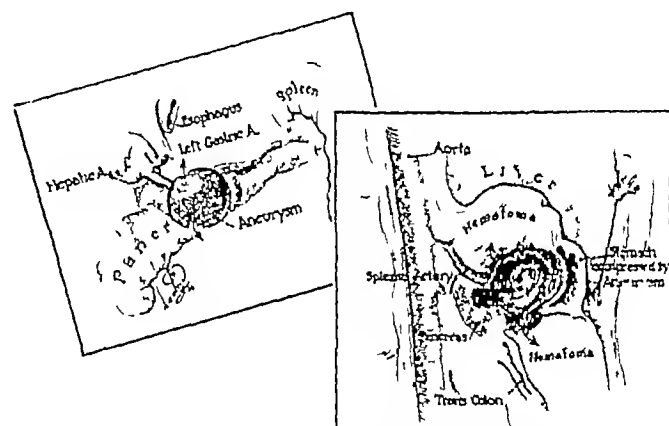


Fig 2 Case 10 Ruptured aneurysm of the splenic artery with massive hemorrhage into the lesser sac

Case 12 *Occlusion of the Splenic Artery* Female, age 55, admitted 12-5-38, died 12-25-38.

CC There was a history of nausea and anorexia for 3 months, emesis for 3 weeks, and loose bowel movements for three days. She had had arthritis deformans for many years.

PE There was generalized edema and anasarca. The heart was not enlarged. The blood pressure was 170/60. The abdomen was distended with fluid.

Laboratory Hemoglobin 68%, RBC 3,540,000, WBC 8,000 to 13,000, with left shift.

Alb 1.5, Glob 5.8

Urine Albumin 1 to 3 plus, WBC and RBC. Culture showed B. Coli.

Stool Occult blood present three times.

Course Gradually downhill.

Autopsy Findings Cases 11 and 12 (Figs 3 and 4). These form an interesting sequence of events.

Case 11

1 Old coronary atherosclerosis and thrombosis

2 Scarring and thinning of left ventricle with aneurysm

3 Mural thrombi in aneurysm

4 Atherosclerosis and mural thrombi of thoracic aorta

5 Embolism from thrombus either of heart or aorta

6 Embolic occlusion of splenic artery

- 7 Anemic infarcts in the spleen
- 8 Descending venous thrombosis of the splenic vein
- 9 Descending venous thrombosis of the portal and superior mesenteric vein
- 10 Recent hemorrhagic infarction and necrosis of upper jejunum

Case 12

- 1 Parietal thrombosis of descending aorta on basis of atheromatosis
- 2 Occlusion of splenic artery
- 3 Anemic infarcts of the spleen
- 4 Thrombosis of splenic vein
- 5 Recent thrombosis of superior mesenteric vein and portal vein
- 6 Anemia and fatty changes of liver with reduction in size
- 7 Arteriolar nephrosclerosis, ascites, right hydrothorax

The similarity of these cases is striking, though in the first, coronary disease is probably a source of the embolus, while in the second, a mural thrombus of the aorta is certainly the cause of the occlusion of the splenic artery. In each of these cases we have joined together atherosclerosis arterial and venous thrombosis, embolism and infarction.

The cases of Mesenteric Thrombosis are summarized in Table II

TABLE II
Mesenteric occlusion

15 Cases		
ACUTE ONSET—12 Cases		
SUDDEN AND AGONIZING PAIN AND EMESIS		
Location	Epigastrium	5
	R.U.Q.	2
	R.L.Q.	2
	L.L.Q.	3
Duration	1 day or less	6
	2 days	3
	3 days	1
	4 days	1
	2 weeks	1
GRADUAL ONSET—3 Cases		

Case 13 Diffuse abdominal pain especially in L.L.Q. Frequent emesis 3 weeks. Sudden shock. Death. Venous thrombosis apparently primary. Hemorrhagic infarction of intestine.

Case 14 Diarrhea and abdominal cramps of varying severity 10 days.

Case 15 Tarry stools and constipation for 8-10 weeks. No pain. Passage of red blood per rectum on day of admission. Died 2 days later.

Case 15 was unusual. Because of the 10 weeks of painless bleeding he was thought to have carcinoma of the colon. Bleeding, noted by sigmoidoscopy above the lower sigmoid colon, was thought to be probably malignant. 2 days later the patient died suddenly and the post-mortem revealed thrombosis of the origin of the inferior mesenteric artery, with recent hemorrhage in the sigmoid and rectum.

The four chief sources of mesenteric occlusion as illustrated in our fifteen cases, are

- 1 Embolism from the heart (fibrillation parietal thrombus)
- 2 Atherosclerosis of the aorta with formation of parietal thrombi which occlude by extension or the breaking off of emboli
- 3 Atherosclerosis and thrombosis of the mesenteric arteries themselves
- 4 Thrombosis of the veins usually on the basis of obstruction

The causes of mesenteric venous thrombosis in our series, were

- 1 Primary carcinoma of the liver with invasion of the portal veins
- 2 Thrombosis of the splenic artery causing splenic infarction

3 Apparently primary

Mesenteric thrombosis often goes undiagnosed and even unsuspected. An attack of colic in any part of the abdomen with few physical signs should make one suspect the condition in a patient with any of the following

- 1 Advanced age
- 2 Marked atherosclerosis
- 3 Auricular fibrillation
- 4 Left ventricular failure
- 5 Evidence of old cardiac infarction—ECG changes
- 6 Presence of embolic phenomena elsewhere
- 7 Absence of premonitory GI symptoms

The pain of mesenteric thrombosis is usually acute,

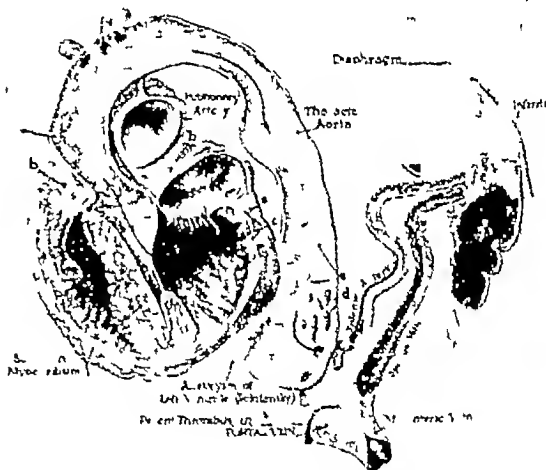


Fig 3 Case 11 Occlusion of splenic artery by embolus from mural thrombus in aneurysm of left ventricle secondary to coronary occlusion. Resultant splenic infarction and descending venous thrombosis of splenic, mesenteric and portal veins

severe knife-like, colicky at first intermittent, but becoming persistent. It may be localized or generalized. Often there is nausea or emesis. Shock of various degrees is usually present. Pain may, occasionally, be gradual in onset as in two of our cases, or entirely absent, as in one.

Physical signs are few early. There may be slight tenderness and spasm. Signs of peritonitis may develop later. Melena not accounted for by a primary intestinal lesion might make one think of mesenteric thrombosis.

Suggestive laboratory findings are

- 1 Leucocytosis of 15-30,000
- 2 Blood in the stools
- 3 Increase in the icteric index, with increase in the quantitative Van den Bergh reaction (indirect), resulting from hemolysis of red cells in the infarct. We have found this test of special value.

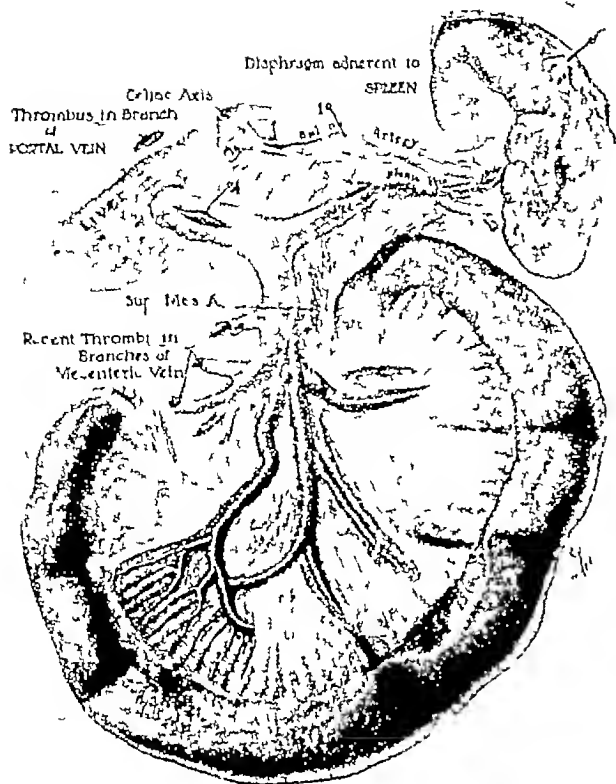


Fig 4 Case 11 Same case as in Fig 3 showing the thrombosis of the splenic artery, the splenic infarct, the thrombosis of the splenic, portal and mesenteric veins and the resulting intestinal infarction

In the majority of cases it is not a question of *wrong* diagnosis, but of *no* diagnosis

SMALL ARTERIAL BRANCHES

Involvement of the small branches of the arterial tree—the small muscular arteries and arterioles—may give rise to abdominal manifestations quite as dramatic and mysterious as does involvement of the aorta or larger vessels. This is demonstrated in this series by

- 1 One case of malignant hypertension
- 2 Four cases of peri-arteritis nodosa

Case 16 Malignant Hypertension with Enteritis and Volvulus A white male, age 30, admitted 2-8-40, died 2-24-40

CC Anorexia, fullness, nausea and emesis, pain and soreness in the abdomen since 2-1-40 (one week)

PH For two years there have been typical clinical evidences of malignant hypertension: high systolic and diastolic pressure, albuminuria, severe headaches, weight loss, blurring of vision, retinal changes, dyspnea on exertion

PE Cardiac enlargement (slight), B P 235/135

Lab Urine—S G 1.012-1.020, Alb 2-4 plus, R B C 2-10

Blood—Urea 29.92 mg/100 cc, R B C 2,400,000, Hb 62%

Course During two weeks' stay in the hospital before his death, the patient's symptoms increased, his abdomen became markedly distended and showed rebound tenderness, absent peristalsis, dilated loops of small bowel with ladder formation, as seen by X-ray, and finally fecal vomiting, rising blood urea, death

Autopsy Findings

1 Recent, extensive, ulcerating, necrotizing enteritis with diffuse necrosis of the lowest portion of the ileum,

and phlegmonous, necrotizing cholecystitis, all due to severe atherosclerotic changes in the arterioles with necrosis of the walls, thrombosis and hemorrhage (Fig 5)

2 Volvulus of the root of the mesentery, twisted 180° to the left

3 Recent diffuse, fetid peritonitis

4 Distinct arteriofibrosis of major branches of the mesenteric artery

5 Arteriosclerotic shrinkage of the kidneys

6 Concentric hypertrophy of the left ventricle

This case is significant because involvement of the arterioles in the intra-abdominal organs other than the kidneys has seldom been described. The changes in the arterioles in this case are purely degenerative in nature.

The four cases of *peri-arteritis nodosa* discussed in this report include three which were diagnosed during life, two of these by exploratory laparotomy, one by muscle biopsy. All four had prominent digestive symptoms which led them to seek medical advice. One had gangrene and perforation of the ileum, so that it was necessary to resect 10 inches of ileum bound in a mass of adhesions.

Peri-arteritis nodosa is a true arteritis of the medium and small arteries and arterioles. There is an endarteritis, a medial necrosis, thrombosis, mycotic aneurysm formation with rupture, hemorrhage and peri-vascular, polymorphonuclear infiltration. The symptoms are toxic and vascular in origin. They are highly variable and depend on the arteries involved. Abdominal symptoms are prominent since involvement of the abdominal arteries and arterioles is a frequent part of the disease.

Case 17 Peri-arteritis Nodosa Female, age 64, admitted 3-11-39, discharged 4-1-39

CC Patient had peptic ulcer at 21, periods of vague dyspepsia since. For the past 9 months she had complained of anorexia, weakness, nervousness, eructations, flatulence, occasional nausea and vomiting, periods of slight diarrhea preceded by constipation, excessive thirst, mild precordial and substernal pain, slight dyspnea on exertion, slight edema of ankles, slight dizziness on rapid change of position, pain in anterior surface of both legs.

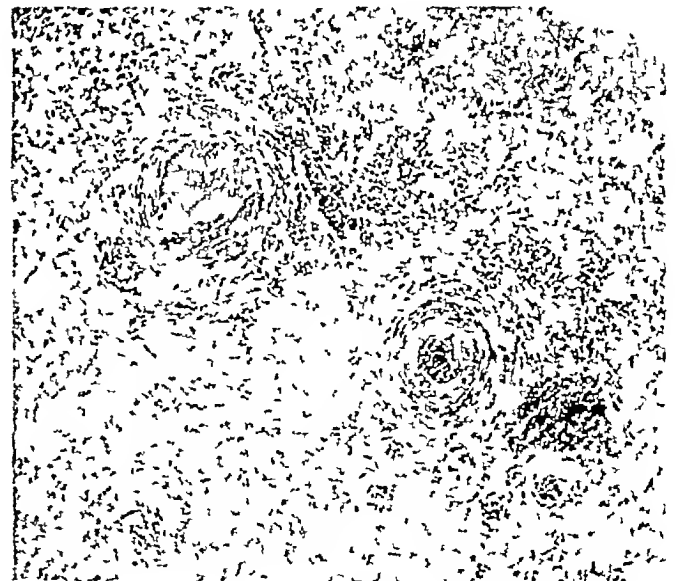


Fig 5 Case 16 Malignant hypertension. Section from ileum. Arteriole showing atherosclerosis, thrombosis, necrosis. Little perivascular reaction.

She was hospitalized in 1938 and showed mild anemia and persistent occult blood in the stools

Since discharge her anorexia has persisted. She has noted also frequent generalized abdominal pain associated with nausea and often emesis and has lost 10 pounds in weight.

P.E. Well nourished, not acutely ill B P 138,80

Mouth Tongue atrophic, beefy red

Chest Emphysematous

Heart Enlarged to left and downward, tones poor, harsh systolic murmur at apex

Abdomen Negative

Laboratory

Urine Trace albumin Rare white and red cells

Blood R B C 4,100,000, Hb 75%, W B C 6,650 Normal differential

Gastric. No free HCl after histamine

Stool Occult blood 1-plus occasionally

X-ray G I Series—gall bladder series negative. Liver enlarged on flat film of abdomen

Course Exploratory laparotomy—no abnormalities found except what appeared to be cirrhosis of the liver. Biopsy of liver and appendectomy performed. Post-operative course uneventful. Complaints have persisted. Patient still alive.

Biopsy report

Appendix Typical peri-arteritis nodosa, most marked in submucous arteries

Liver Very distinct changes of peri arteritis nodosa in a rather acute stage in some arteries within the portal spaces. Distinct interstitial non-specific inflammation with many eosinophiles

Gastroscopy 10-3-39 (performed by Dr Harry Murphy). Entire stomach was well visualized. The pylorus appeared normal. In the antrum the mucosa showed a peculiar nodular surface. The color was normal. At the angulus this nodular formation was accentuated particularly on the anterior aspect and extending toward the greater curvature. These nodules were smooth shiny, and somewhat redder than normal. On the anterior wall a most unusual picture was seen. In a somewhat patchwork pattern, there were areas of reddened slightly elevated but rather smooth mucosa, and interspersed between these areas were thinner areas of decidedly gray mucosa. It gave somewhat the appearance of geographical relief map with small reddened elevations and gray valleys. On the posterior wall this change was present but not so marked. In the uppermost portions of the stomach the mucosa was entirely gray, and large blue branching blood vessels were visible.

Impression From the gastroscopic picture alone I am unable to make a diagnosis. However, in view of the reported biopsy studies, I would assume that these changes are due to peri-arteritis nodosa.

Case 18 *Peri-arteritis Nodosa* Male, age 42, admitted 10-24-40, died 3-5-41

C C

1 For past 3 weeks he has had severe aching pain, worse after eating, not relieved by alkalies becoming progressively worse, also anorexia, nausea, occasional emesis. For 6-12 months he has had some discomfort and fullness after eating regardless of size and kind of meal, also moderate diarrhea. He has lost 30 pounds in the past year.

2 Painful red areas noted on both feet and both hands for past 4 weeks.

3 Psoriasis many years. Asthma past 5 years.

P.E. Chest. Sibilant and sonorous sounds. Rhonchi.

Heart Systolic bruit over precordium B P 157/76

Abdomen Soft, distended veins, cephalad direction of blood flow. Liver enlarged to umbilicus sharp edge, smooth, non-tender. Spleen not palpable. No other masses. Palpable inguinal nodes.

Extremities Tender sole of right foot. Psoriasis of forehead and elbows.

Laboratory

Urine Albumin 1-plus, glucose 1-plus, occasional W.B.C., R B C and casts

Blood R B C and Hb normal, W B C 55,000-33,000 first month, Eos 44-74%, W B C 15,000-30,000 next 4 months, Eos 46-52%. Blood chemistry normal. Serology negative. Blood culture negative.

Stools 1-plus, 4-plus and negative for occult blood.

X-ray Large ulcerating lesion of lesser curvature of stomach.

Gastroscopy "On lesser curvature there is a medium sized, punched out ulcer with dirty yellow necrotic base. No evidence of malignancy noted."

Course Frequent crops of petechiae on lower extremities characteristic of peri-arteritis nodosa. Frequent asthmatic attacks during hospitalization—fairly well controlled with Aminophyllin. Sudden cerebro-vascular accident (convulsion, coma, Cheyne-Stokes breathing). Died 9 hours later.

Biopsy report Biopsy of muscle made soon after admission. Pathological report on biopsy histological find-



Fig 6 Case 19 Peri-arteritis nodosa of mesenteric arteries showing characteristic nodule in wall of small intestine

ings in I vessel indicate changes as seen in peri-arteritis nodosa with marked inflammation of wall showing particularly eosinophilic infiltration and with occlusion of lumen. Diagnosis based on biopsy. No autopsy.

Case 19 *Peri-arteritis Nodosa of the Mesenteric Arteries* Male, age 48, admitted 5-1-40, died 6-20-40

C C

1 He has had constipation and lower abdominal cramps for past 2-3 days, relieved by 2 doses of salts. Involuntary, watery stool and emesis this a.m.

2 Two weeks ago he was forced to go to bed because of severe pains and weakness in legs, has remained there since.

3 He has been in poor health the past year, easy fatigability, hypertension.

P.E. Patient admitted in shock. Cold, clammy hands, cyanotic low B P, almost imperceptible pulse. Coarse rales in bases. Some tenderness R L Q, ECG not remarkable. During first day B P rose gradually to 192/134.

Laboratory

Urine Trace albumin, moderate number red and white cells.

Blood Albumin 3.0, glob 2.5, urea N 11, agglutination tests negative.

Leucocytes 17,000-47,000 entire course, R B C and Hb normal, Polys 80-90%, Bands 28-58%

Skin test for trichinae Negative

Course Indefinite and confusing throughout 5 weeks hospitalization Abdominal discomfort and anasarca almost constantly present Abdominal tenderness and distension frequently changing in location and character Several bouts of diarrhea—watery (average 2-4 per day) Occult blood 0-2 plus, occasionally 4 plus Pulmonary congestion on several occasions Pulmonary infarction on one occasion Fever elevated to 102° per rectum daily X-rays of colon (enema) attempted after 4th week Immediately following this, passed fresh blood clots per rectum over a three day period Went into shock Died

Autopsy Findings (Figs 6, 7)

1 Peri-arteritis nodosa of the mesenteric arteries, especially at the attachment of the mesentery to the intestine, with pea-sized, firm enlargements of the arterial wall

2 Scattered recent and older ulcers and erosions of the ileum

(Bands 40%, filaments 45%), Lymphs 8%, Monos 7%, Sedimentation rate 6 mm in 1 hour

Course Laparotomy 9-24-39 Inflammatory mass, including 10 inches of ileum was resected from the L L Q Septic picture developed after operation Death three weeks later

Pathological Findings Gangrene and perforation of the entire bowel wall due to acute arterial inflammation belonging to the polyarteritis or peri-arteritis group

The gross and histological characteristics of peri-arteritis nodosa are illustrated in Figs 6 and 7

Peri-arteritis nodosa should be suspected in a case presenting Evidence of infection (leucocytosis, fever, etc), plus abdominal symptoms, plus unrelated symptoms of widespread involvement of other parts of the body, such as asthenia, neuritis, myositis, kidney disease, hypertension

The diagnosis is made by laparotomy and biopsy Three of our cases were so diagnosed during life An unexplained eosinophilia should lead one to think of

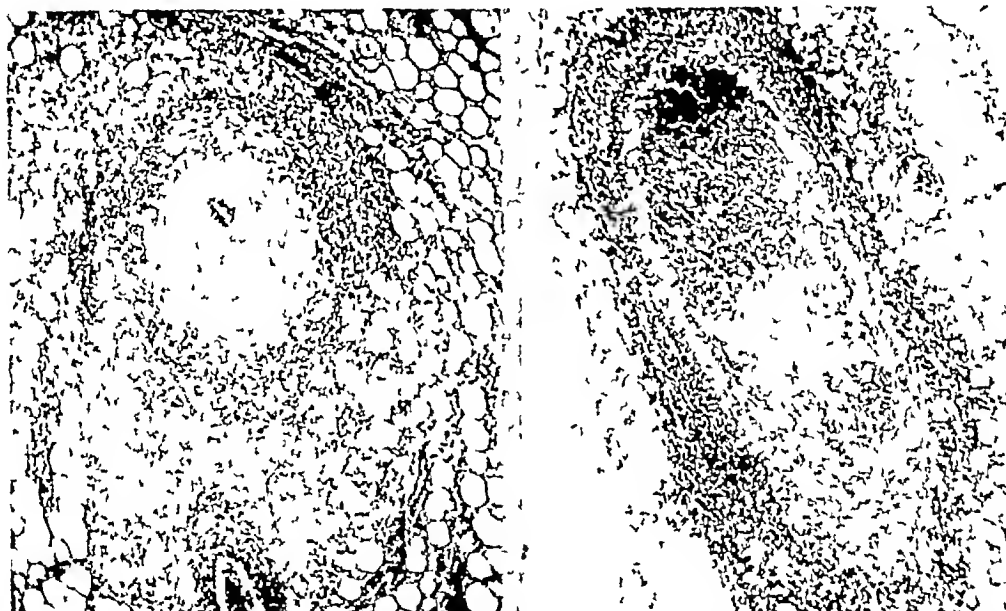


Fig 7 Case 19 Peri-arteritis nodosa of mesenteric arteries Same case as in Fig 6 Two sections that on the right hand shows an acute stage with thrombosis and marked peri-arterial infiltration, that on the left shows a chronic or "healed" stage with almost complete obliteration of the artery

3 Aneurysm of the cystic artery with complete thrombosis

4 Infectious splenic tumor

5 Purulent bronchiolitis and lobular pneumonia

Case 20 *Peri-arteritis Nodosa Causing Intestinal Gangrene and Perforation*. White female, age 47, admitted 9-18-39, died 10-15-39

CC Attacks of mild epigastric pain noted for 3-4 days, every 4-6 months, for past 6-7 years, no nausea or emesis Three weeks ago she awoke at 4 a m with severe epigastric and umbilical pain accompanied by nausea and vomiting This lasted three days It recurred again three days later and yet again for three days preceding admission No change in bowel habits Stools always brown Patient has had chronic deforming arthritis for 27 years

PE T 98.6° Evidences of old rheumatoid arthritis Chest clear, heart negative B P 160/104

Abdomen Marked tenderness in both lower quadrants, especially the left. Peristalsis present

Pelvic. Round, very tender mass in left cul-de-sac

Laboratory

Hb 83%, RBC 4,400,000, WBC 18,000, Polys 85%,

periarteritis (Case 18) Felsen (3) has shown the usefulness of sigmoidoscopy in establishing the diagnosis He employs a telescopic lens and red and green filters Gastrosocopy in one of our cases gave a unique and suggestive picture

VEINS

This series of cases includes instances of thrombosis of the inferior and superior mesenteric, splenic and portal veins, the iliac veins and the vena cava

Venous thrombosis secondary to carcinomatous invasion of the veins is shown in cases 21 and 22

Case 21 was a male, age 58, with multiple abdominal metastases from primary carcinoma of the stomach There was an infiltration of both common iliac veins by carcinoma and a complete obliterating thrombosis and beginning organization of both common iliac veins The result of the obstruction of the iliac veins was edema of both legs for ten days before death Of interest in this case was the marked distension of the abdomen early and throughout

the disease. This was thought to be due to the infiltration and replacement of the celiac ganglia by metastases.

Case 22 was a male, age 59. Autopsy revealed a diffuse, nodular cirrhosis of the liver, with primary liver cell carcinoma on the basis of cirrhosis, carcinomatous thrombosis of the portal vein within the liver and of both extra-hepatic branches in the hilum of the liver and of the portal vein proper, marked hemorrhagic ascites (8,000 cc), moderate splenic tumor, distinct esophageal varices, metastases to the lungs.

Cases 11 and 12 previously cited, were examples of descending venous thrombosis due to splenic infarcts resulting from occlusion of the splenic artery.

Case 13, also previously cited, was an instance of mesenteric venous thrombosis—apparently primary—with hemorrhagic infarction of the intestine.

One case worthy of special mention was a case of Banti's disease due to organized thrombosis of the splenic vein.

nation for the development of some of the typical instances of Banti's disease.

SUMMARY

A summary of 40 cases of disease of the large and small intra-abdominal arteries and veins has been presented. These have included aneurysm of the abdominal aorta (atherosclerotic dissecting and luetic) and aneurysm of the splenic artery, occlusion of the aorta, the superior and inferior mesenteric arteries, the splenic and left gastric arteries, the inferior vena cava and iliac, portal and splenic veins. In addition there were included 4 cases of peri-arteritis nodosa and one of malignant hypertension. All of these cases have presented symptoms and signs pointing to intra-abdominal disease. An attempt has been made to emphasize by case reports the chief varieties of disease of the intra-abdominal vessels together with some helpful diagnostic hints. Certain cases of unusual

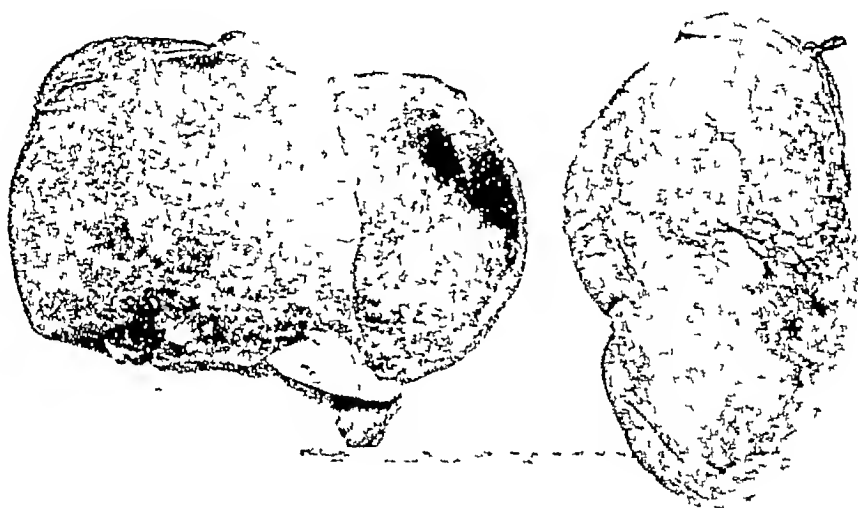


Fig 8 Case 23 Banti's disease showing (left) smooth cirrhosis of the liver and (right) enlarged fibrosed spleen associated with calcified thrombosis of splenic vein

Case 23 Banti's Disease Due to Organized Thrombosis of the Splenic Vein. A white male, age 43 at final admission, 1940, had had 7 admissions from 1930-1940 for hematemesis, large liver and spleen, with anemia and leucopenia. History of malaria in 1914 and of having been kicked by a horse in the left side of the abdomen. On his last admission, Hb was 44%, RBC 2,200,000 WBC 4,400 Van den Bergh 18 mg %. Had further hematemesis while in hospital, developed pneumonia and died.

Autopsy Findings (Fig 8)

1 Calcific organization of thrombotic sclerosis of splenic vein with modified calcific sclerosis in portal vein without obstruction

2 Splenomegaly with increased fibrosis of the spleen (Banti's disease)

3 Smooth cirrhosis of the liver with slight atrophy

4 Esophageal varices

5 Diffuse entorrhagia

6 Early pneumonia and atelectasis of both lower lobes

It is interesting to speculate whether or not the kick by the horse could have damaged the splenic vein and have led to the calcific thrombosis. The calcific thrombosis of the splenic vein certainly led to the development of "portal hypertension" which is the expla-

interest clinically or pathologically have also been detailed.

CONCLUSION

Vascular diseases within the abdomen may give rise to acute and chronic abdominal symptoms. Vascular disease in this location is often misdiagnosed or unsuspected by both physician and surgeon. It may be overlooked even when the abdomen is opened. The error more often is one of no diagnosis than of missed diagnosis. The diagnosis could be made more frequently if the possibility of vascular disease were considered. This is especially true in the presence of acute abdominal episodes. The vascular origin of abdominal symptoms must be considered in the presence of (1) arteriosclerosis (2) nodular fibrillation (3) previous coronary disease or cardiac failure, (4) evidence of emboli elsewhere. Laboratory tests which in our experience may give a hint of intra-abdominal vascular disease are (1) increase in the quantitative Van den Bergh reaction. This may aid in the diagnosis of mesenteric and other forms of thrombosis. 11

is the result of hemolysis in an infarcted area, (2) unexplained eosinophilia. This should lead one to rule out peri-arteritis nodosa as a possible cause.

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DISCUSSION

CAPTAIN J EDWARD BERK (Fort Dix, N J) In 1939 we had the occasion to observe a fifty-two year-old man who presented the signs and symptoms of an acute abdominal catastrophe. At operation there was found an abdomen filled with unclotted fresh blood. After this was thoroughly evacuated, no bleeding point could be found. The patient went on to a rather complete recovery.

Because of the absence of any history of trauma preceding admission to the hospital, we felt that we were dealing with an example of a spontaneous non-traumatic rupture of a small intra-abdominal blood vessel, a condition to which others had given the name "intra-abdominal apoplexy." This name was purposely chosen in order to indicate the close similarity to the more common and better recognized cerebral apoplexy.

In the literature at that time we could find but nineteen other seemingly similar cases. Since then Dr Crile, Jr, has reported another.

A review of the clinical features of these cases revealed some interesting findings. The outstanding feature was the existence of either hypertension of a severe degree or a generalized arteriosclerosis in about 60 per cent. In the older age group, in whom hypertension and arteriosclerosis was common, a bleeding point in the abdomen could usually be found and ligated and recovery usually ensued. In the younger age group, in contrast, in whom hypertension and arteriosclerosis was uncommon, bleeding points were not usually found and the mortality rate was much higher.

The commonest pre-operative diagnosis was perforated peptic ulcer, in every instance the finding was a complete surgical surprise.

I feel that this very fine report this morning will establish on a much sounder and more secure basis what hitherto has been considered as a rare and unusual but interesting clinical occurrence.

DR ROBERT ELMAN (St Louis, Mo) This is a very important contribution and I should like to make one comment and that is that surgeons will miss many of these conditions unless they explore the abdomen thoroughly at the time of operation, I remember a number of cases I have operated upon which would fall into the group of patients that have been discussed this morning.

Another important thing surgically, it seems to me, is to express a note of conservatism, i.e. that very little be done to the intestines of these patients once the diagnosis is made, unless there is irreparable necrosis or obvious

gangrene. Most of the patients have lesions which seem to recover spontaneously even if nothing is done at the time of operation, as illustrated by one or two of the patients discussed this morning.

DR JOSEPH FELSEN (New York) Mr Chairman, Ladies and Gentlemen. I cannot let this opportunity go by without complimenting Dr Kimball and his co-workers on a very excellent piece of work. I am very much interested in their observations and have had the pleasure of discussing them with Dr Kimball. The sigmoidoscopic diagnosis of systemic disease is a virgin field which we as gastro-enterologists should undertake with a proper understanding of its potential value in medicine. Two of the cases which Dr Kimball presented illustrate this point very nicely.

Intestinal vascular sclerosis, which is a simple descriptive term for one of the conditions described, is very easily diagnosed by sigmoidoscopy. Seen through a clean intestinal mucosa, the appearance of the intramural mesenteric vessels corresponds to that of the retinal vessels. Thickening, tortuosity or obliteration may be noted, depending upon the degree of arteriosclerotic change.

The second condition mentioned by Dr Kimball to which I shall refer is peri-arteritis nodosa. The case shown was first diagnosed during life at sigmoidoscopy. Frankly, when first seen, the sigmoidoscopic picture of localized, intramural, segmental vascular thromboses, was completely new to me. During the course of several hundred sigmoidoscopic examinations for intestinal signs of systemic disease, it had never been encountered. For comparative study it was therefore deemed advisable to review all intestinal museum specimens which exhibited vascular pathology. Fortunately, two examples of intestinal lesions in peri-arteritis nodosa were in my collection. They corresponded exactly to the condition noted in the living patient. Neither of the two patients who came to necropsy had been sigmoidoscoped during life, however. After several examinations, it was apparent that the lesions in the living patient were persistent, could not be obliterated by pressure and exhibited distal hair line vascular threads devoid of blood. A diagnosis of peri-arteritis nodosa was made and final proof of its validity was offered six months later, after the patient had been followed through Montefiore, Bellevue and Mt Sinai Hospitals. The necropsy specimens were made available through the courtesy of Dr George Bachr and Dr Paul Klemperer and revealed the gross lesions described during life with confirmatory microscopic evidence of peri-arteritis nodosa.

DR STOCKTON KIMBALL (Buffalo) (closing the discussion) I want to thank the discussers for their very generous discussion. We had one case that well illustrated the abdominal apoplexy, mentioned by Captain Berk, a case of thrombosis of the splenic artery with rupture and hemorrhage.

Two of the cases of mesenteric thrombosis were not recognized when they were opened by the surgeon, so that the diagnosis may be missed not only pre-operatively but even at the time of operation.

Notes On Nutrition

The Armed Forces of the U S A are the best fed fighters in the world. Daily army garrison ration, May to October 1941—Cal 4331, protein 131 g, fat 195 g, carbohydrate 513 g, calcium 1.01 g, phosphorus 2.03 g, iron 25 mg, vit A 13,270 I U, thiamine 2.0 mg, riboflavin 2.8 mg, nicotinic acid 29.6 mg, ascorbic acid 97 mg. Adequate food, with scientific attention to its constitution will go far in pro-

tecting fighters from the heavy toll on their physical and nervous stamina (J A M A, 120 93-96, 1942).

Niacin (nicotinic acid) is present in beef, pork, veal and chicken livers in amounts ranging between 100 and 152 micrograms per gram, and in muscle meats from 60 to 70 micrograms per gram. Chicken breast contains 151 micrograms per gram, which thus appears to be good news for persons dishing spinach.

Beef, lamb and veal kidneys contain from 77 to 95 micrograms per gram. Rabbit tissues are high and fish are, as a rule, low in niacin. Peanut butter is an excellent source of niacin, containing 186 micrograms per gram. These facts, as revealed by new methods of analysis (a modification of the cyanogen bromide method) are of importance in pellagra areas (J. Nutrit., 24 153, 1942).

Intestinal Bacteria, regarded since Metchnikoff as rogues, may have a distinctly beneficial effect, in view of recent work which indicates that many of them are able to synthesize B vitamins in vitro, and may be presumed to manufacture these vitamins in the intestine in at least moderate amounts. This may explain why babies on cow's milk do not show evidence of lack of nicotinic acid even though milk is poor in this agent. *Escherichia coli*, normally a dominant organism in the human intestinal flora, produced the most riboflavin, *Alcaligenes fecalis* the most thiamine, and *Bacillus mesentericus* the most nicotinic acid (Proc. Nat. Acad. Sci., U.S., 28 285, 1942).

Tooth decay. A well-controlled clinical experiment showed that Vitamin D has a beneficial effect in retarding dental caries, and suggested that Vitamin D from cod liver oil was about twice as effective unit for unit, as radiated ergosterol. Even 800 units (USP) of Vitamin D from cod liver oil did not fully protect from caries (J. Am. Dental Ass'n., 29 1393, 1942). D from animal sources is D₃ and that from plant sources is D₂. Perhaps the length of the experiment was not enough to permit conclusions. There is still no consensus of opinion on the causes and control of tooth decay.

Muscle Dystrophy and Vitamin E deficiency. Although E deficiency had a marked influence on muscle metabolism in experiments on mice, it had no effect on spermatogenesis and it would appear that E is probably not, as formerly thought, effective against sterility, but essential to normal muscle metabolism (Am. J. Path., 18 169, 1942).

Vanadium was sought in vain in many animal tissues and in foods used by animals and previous reports of traces of this element in biological materials probably were in error arising from a now-demonstrated fault in technique (Am. J. Physiol., 136 772, 1942).

Vitamin A in liver was estimated in the liver sold in butcher shops in England, and sheep's liver was found to have the highest and most constant amount of all with little seasonal variation as in beef (Biochem. J., 36 34, 1942).

Withholding *potassium* in the diets of rats produced marked myocardial degeneration as well as similar changes in the convoluted tubules of the kidneys, confirming earlier work which showed that lack of dietary potassium could cause cardiac lesions (Am. J. Path., 18 29, 1942).

Wheat germ contains high concentrations of thiamine, riboflavin and pyridoxine, but low amounts of niacin and pantothenic acid. A high milling loss was found for niacin, pantothenic acid and pyridoxine in flour made from wheat (J. Nutrit., 24 167, 1942).

Cobalt and copper fed to bled dogs not deficient in either gave results suggesting that in recovery from hemorrhagic anemia there is an optimum level of copper intake, and that cobalt has a retarding effect on hemoglobin formation (J. Exp. Med. 75 481, 1942).

Industrial war workers' food has so far been a hit and-miss affair and if you want to know how bad it has been and good it can be made, write for the report to Dr. Frank Gunderson, Food and Nutrition Board, 2101 Constitution Ave., Washington, D. C.

Grapefruit is a source of ascorbic acid, but like oranges, they contain variable amounts which depend, to some extent, on sun-exposure but not at all on the locality in which they are grown (J. Agr. Research, 61 57, 1942).

Pyridoxine injected into patients intravenously raised the muscular fatigue threshold in some and had no effect in others, which does not recommend the procedure at this time. (J. Lab. and Clin. Med., 27 763, 1942).

Calcification of the heart seems to be an increasing function of age, and auricles were more frequently affected than ventricles and valves. Fat rats, doing moderate exercise showed more calcification than normally nourished ones forced to exercise. (Am. J. Path., 18 41, 1942).

Vitamin A and tuberculosis, it was found that persons having tuberculosis associated with varying degrees of intestinal symptoms absorbed Vitamin A poorly as compared with normal persons. Autopsies showed no pathological condition of the intestines to which such faulty absorption might be attributed, but obviously persons with the disease require above average amounts of Vitamin A (J. A. M. A., 119 3, 1942).

Thiamine deficiency in man is more likely to be reversible and amenable to specific therapy when the disease has come on suddenly and acutely but is less so when the disease has been milder in onset more chronic and attended by widespread degeneration of nerve fibres (Arch. Neurol. Psychiat., 47 97, 1942 and ibid 47 626, 1942).

Tomatoes and cabbage. When ripe, tomatoes have more ascorbic acid than when immature, but cabbage has irregular amounts. Certain varieties produce more ascorbic acid than others (J. Agr. Research, 64 433, 1942).

Aritaminosis A in Dairy Calves. Constriction of optic foramen with pressure on optic nerve, blindness as well as enteritis and testicular degeneration, are among the results found in this condition (J. Nutrit., 17 443, 1939), (Am. J. Vet. Res., 3 27, 1942).

Lack of *biotin* in human diet produced mild dermatitis, pallor due to vasoconstriction, and atrophy of the lingual papillae, lassitude, anorexia, cardiographic changes, hemoglobinemia, and these were cured by administration of biotin rapidly. Egg white binds biotin, a member of the Vitamin B complex. (J. A. M. A., 118 1199, 1942).

Experimental *hypertension* in dogs produced by constriction of the renal arteries responded strikingly to large doses of Vitamin A—a possible pharmacologic action of A, but one which would not necessarily be effective in clinical hypertension of the non-renal type (Science, 96 161, 1942).

Vitamin K seems important to the maintenance of normal levels of blood prothrombin, as animals deprived of dietary K invariably aborted because of low levels of prothrombin. A. J. Obst. and Gyn., 43 1007, 1942).

The human *thiamine requirement* minimum is 0.5 mg per 1000 calories, optimum between 0.5 and 1.0

mg per 1000 calories (Arch Int Med, 69 721, 1942), (Am J Med Sci, 203 569, 1942), (J Nutrit, 24 139, 1942)

Wernicke's syndrome (clouding of consciousness, ophthalmoplegia and ataxia) is similar in pathology to that seen in thiamine deficient pigeons, and therapeutic experiments with the clinical disease indicate that Wernicke's syndrome is associated with a disturbance in pyruvic acid metabolism and thiamine deficiency. Thiamine therapy was found to cure the

ocular palsies and often improved the mental state (Arch Neurol and Psychiat, 47 215, 1942)

Rats, deprived of Vitamin B₁, tend to show *epileptoid convulsions*, but we must not attribute this manifestation to the elimination of a single nutrient and clinically the administration of pyridoxine (Vitamin B₆) to human epileptics has not been encouraging in its results (Science, 95 331, 1942), (Biochem J, 34 594, 1942), (J Comp Psych, 31 215, 1941)

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Editorials

FATIGUE

SIDNEY A. PORTIS, M.D., of Chicago, addressing The American Society for Research in Psychosomatic Problems on December 18, 1942, gave a report of some preliminary studies in the mechanism of fatigue in neuropsychiatric patients. Previous research had shown that stimulation of the right vagus nerve had resulted in hypoglycemia, through a presumed stimulation of the pancreatic function resulting in hyperinsulinism. This phenomenon occurred only when the right vagus was intact and it was found that the mechanism responsible could be upset palpably by the administration of atropine prior to vagal stimulation. In a number of neuropsychiatric patients referred to him by the psychiatric service for the purpose of discovering, if possible, some cause for the weakness of which they complained, he carried out blood sugar curves following the intravenous injection of less than one gram of glucose. In all cases a noticeably flat type of curve was found after glucose injection the rise in blood sugar level was small, and, after two hours, a drop below the pre-injection level frequently was noted. On the theory that these individuals were suffering from hyperinsulinism, Portis repeated the blood sugar curves in the same manner, after the patients were under the influence of atropine. In these cases, more nearly normal blood sugar curves were obtained. A regimen of frequent feeding with carbohydrate and the administration of atropine over a period of several weeks or months resulted in marked improvement of the fatigue of which these patients previously complained, permitting them to assume normal work and responsibilities without inconvenience. Because of other physiological experiments in which thalamic stimulation, with intact right vagus, had resulted in hypoglycemia, presumably due to hyperinsulinism, it was possible to believe that, in nervous patients, worry and anxiety had reproduced the stimulation of the thalamus which, being propagated via the right vagus fibres, had created a chronic hypoglycemia with its resulting weakness and fatigue.

The clinical results of this experiment are important and highly stimulating to those interested in fatigue in neuropsychiatric patients, and the theory advanced to explain their weakness is not only well supported by the results, but is of great importance in helping to strengthen the suspicion that the vagus nerve is a channel which brings mankind no little trouble. Furthermore, this work, even by its preliminary report, lends support to the broad thesis that mind directly affects body.

The inaugural meeting of the American Society for

Research in Psychosomatic Problems was held on December 18, 1942, at the Waldorf-Astoria Hotel, New York City, the scientific program being devoted entirely to the study of Fatigue in its many aspects. Hallowell Davis, M.D., Professor of Physiology, Harvard University School of Medicine, outlined the plan of the study in his introductory remarks. S. S. Stevens, Ph.D., Assistant Professor of Psychology, Harvard University, dealt with "Psychomotor Performance in the Study of Environmental Stress" while William Forbes, Ph.D., Assistant Director of the Fatigue Laboratory at Harvard University dealt with "Problems Arising in the Study of Fatigue." These, as well as other papers, stressed the difficulty encountered in obtaining a suitable method of measuring fatigue. It is the present plan of the new society to hold an organizational meeting in May, 1943. The recent meeting was held in conjunction with the 23rd Annual Meeting of the Association for Research in Nervous and Mental Diseases.

CONSTITUTIONAL INADEQUACY

THE term "constitutional inadequacy" seems to mean "naturally not up to the job of being well, physically, mentally, and perhaps socially." It is questionable if the term is much of an improvement over older ones. Its looseness of application renders it a little dangerous in the hands of the inexperienced, merely creating another waste-basket for clinical scraps, and giving the stop-signal to further study.

Twenty years ago, a person exhibiting *rumination* was said to give evidence of constitutional inadequacy of the gastro-intestinal tract. The older Italian authors regarded *achylia* as of the same significance, although today we do not feel that this physiological delinquency is often of serious importance. Certainly, the term is not justifiable when applied to any special system deficiency which the patient may be discovered to possess, because otherwise we might speak of many metabolic disturbances as evidences of constitutional inadequacy.

Currently, the diagnosis of constitutional inadequacy is used for persons whose endless complaints have no basis in perceptible pathological lesions and whose response to treatment is only temporary. The individual's discomfort characteristically migrates from region to region. He is hypersensitive to pain. He may or may not be weak physically or mentally. He may or may not lack industry, resolution and courage. His most constant manifestation is perhaps

an undue reaction to distress which might not register on the sensoriums of the phlegmatic. He has not changed in the course of time, or from the day, when he was usually called a "neurotic."

The writer would rather be told that he was "neurotic," for this would stimulate him. It also would console him, for we have been assured by the psychologists that a person is of little consequence unless he is neurotic. But the diagnosis "constitutional inadequacy" would start a quarrel with his ancestors, and might have much too final a sound for his own hope.

Most patients are indifferent to a diagnosis, and seek only assistance in their distress. Therefore, from the public standpoint, it matters little what we call these people, so long as we somehow help them. When faced with a patient across the table in our consulting room, it is perhaps beyond the province of medicine to use a social criterion or tabulate the fact that the neurotic is not an industrial success. However, he may be charming, talented in the arts, capable of deep friendship, or he may be disgusting without talent of any sort, and shift in his loyalties. He is often colorful, pathetic in his apologies for intrusion upon our time and very much in earnest about one thing—his physical and mental discomfort.

Physicians cannot always be criticized when they fail to help him. But we are to blame if we spend all his money on a diagnosis or recommend useless procedures. In the matter of diagnosis, why use Latin words, when Abenethy so beautifully avoided scientific cant in his famous Anglo-Saxon dictum—"Madam, you lack firmness of mind."

Can we assume that these patients have something wrong with their brains? So far we have not seen any review of autopsy findings on the brains of neurotics. Surgical attack on the cerebrum for the purpose of altering personality is so far famous chiefly for its intrepidity. Vitamin B injected intravenously has done some good to nervous persons, probably those who previously lacked the complex. Later some super-essence derived from food concentrates might conceivably be used successfully either intravenously or *per os*. If eugenics ever becomes a popular plaything, selective mating might eliminate some of the neurotics, and bring society nearer to that deadening ideal of a perfectly standardized mob of like-thinking people. Practically, psychiatry has really done some good in helping certain neurotics to get hold of themselves and psychiatry should be encouraged. The private physician must use a combined attack—physiotherapy, mental encouragement, endless patience, as well as a balanced diet, vitamins and drugs. He must not expect brilliant results. It matters very little what phraseology or nomenclature he chooses for the diagnosis, but the one adopted from psychology seems as good as any.

WHAT SOCIALIZED MEDICINE OFFERS

THE Beveridge Report, recently publicized in England, seems to have met with general approval in that country and in Canada as well. It seems to represent as close an approximation to the demands of British socialism as the capitalistic vote of Commons can tolerate and a move sufficiently leftward to satisfy the majority of middle class voters. In Canada it may be approved by the liberals, readily accepted by the

increasingly numerous CCF (Canadian Commonwealth Federation), and it will not be too violently opposed even by the conservatives who at present are looking both for a leader and a program. It will be opposed by such vested interests as industrial insurance and by a severely taxed capitalistic class. The British medical profession, inured to the "panel" type of controlled practice for thirty years, scarcely may be expected to raise effective opposition although the new sweeping reforms must add to their burden of dissatisfaction.

Canada has not always followed England in social innovations, and may not do so now, but the Beveridge Report has created a somewhat favorable impression already in the Dominion. The Canadian profession agree that they can see "the handwriting on the wall," and yet there appears to be no organized effort on the part of the Canadian Medical Association against what may come. The first organizational steps in a broad plan of insurance medicine in Canada probably will have been taken and the machinery put to work long before physicians serving overseas return from war. Even the less purely medical plans for pensions, salary protection in illness, indemnities for birth and death expenses, and employment schemes, seem either to have met with quiet favor, or to have failed to inspire any organized opposition.

The affairs of Canada can well be managed by Canadians and these observations are not made in criticism of our brother physicians to the North, but because at present what Canada does holds a novel interest for us. During the past year, Ottawa has exerted a dynamic influence on the government at Washington, because of a mutual agreement between the two nations to compare notes both on war and peace. Canada's system of taxation and her successful administration of price control has been an object lesson to the planners in Washington. Today scarcely anything is done by either country without the other's knowledge. If the philosophy of the Beveridge Report becomes accepted in Canada, then Washington, already committed to an anti-capitalistic program, would receive renewed inspiration.

This Journal will not spend time in ordinary political argument, but there are extraordinary socialistic changes on the horizon which may deeply affect every medical specialty. The National Physicians' Committee, with the blessing of the American Medical Association, is affording us some protection at a time when the war urgency permits us to think of little else. At such a time, the proponents of controlled medicine will be likely to strike with vigor under cover of the national emergency. Those opposing state medicine, contract medicine and the various forms of insurance medicine which have been advocated or tried, are aware that the present administration has been influenced for many years by the petulant demands of several wealthy socialistic foundations, and that this administration, in its puzzling war time crusade against "trust" monopolies, is attacking medicine from such a fictitious angle. If the supreme court of the land can hold that the profession of medicine is a trust, then we are justified in using or adapting to our use the protective practices of trusts. We realize that now, and in any event, undesirable alterations in practice are almost at hand and that we are not in the best position to oppose renewed efforts at this time.

The National Physicians' Committee urges us all freely to petition and indoctrinate our congressional representatives against all ill-considered schemes which must lead to unfortunate innovations. Our most urgent duty is to ensure that the management of medicine shall remain under the control of doctors of medicine. Even if this can be accomplished, the loss of the profit motive will give birth to a power motive which will soon claim many disciples among our group. Socialized medicine, in spite of good management, will impair the ancient charm of our healing art, blunt our motives, and give the public a service which leaves very much to be desired.

State controlled education was bitterly opposed by the teachers who taught under the system of private education. While the public schools have brought the rudiments of education to millions otherwise unable to afford instruction, the resulting standardization has given us a product which is itself standardized. It has been pointed out that our country is poor in leaders of peak ability, and in literary genius, and that we see now a downward trend in public morality and increase in crime, divorce and the psychoses. While it is illogical to attribute all such results, even if factual, to a single cause, the public school system lacks, and will always lack, a skilful individualization of its work. Specialization exists but it is applied in special cases as a result of a mass method of allocation. The time has not arrived when a Binet-Simon test can constitute an accurate appraisal of a human being. I Q'S and screen tests fail to tell us all that resides within the crania of men and women. The efficiency of public school systems can be seen in the astonishing collection of statistical data and in the bewildering heterogeneity of the curricula, but the state system is not remarkable for producing individuals of original opinions, or for having discovered a satisfactory formula for the social and political requirements of the nation.

A survey of controlled medicine throughout the world leaves an impression similar to that created by controlled education. The State has brought medical care of a type to persons previously unable to afford it, but the quality of the medical work involved is inferior. There is a lack of diagnostic finesse and of therapeutic individualization. British panel doctors frequently manage to maintain an intelligent level of practice, but these exceptional ones will confidentially admit the impossibility of remaining "personal" in their contact with patients. Because of the secretarial duties involved in government reports and the "grind" resulting from the hours spent each day with such large numbers of patients, they find themselves the weary slaves of a tiresome system. Refined diagnosis is impossible because of time limitations.

If State medicine is adapted to America, the public, now accustomed to a highly individualized approach, will be vainly looking for a commodity which will have been not only rationed but driven from the market. Financially the only physician who will benefit from such a system is the one now unable to make a living. All physicians under such a plan will be increasingly regarded, not as the teachers of humanity, but their paid servants. In London today, apart from the few distinguished and titled men who practice privately on Harley or Wimpole Street, the profession enjoys

approximately the same social prestige as shop clerks and piano tuners.

The American physician has always been a "rugged individual" spiritually, if not financially. He has been noted for his self-determination and lack of cooperation with other physicians. There is no better example under the sun of undying love of argument than the proceedings of an average county medical meeting. Lawyers are little better, though they have an official opportunity in court to sublimate pugnacity. The master of the old private school was as full of seasoned individuality as a grandfather's clock. The male teacher in our school system today is of the managerial type, cautious in the expression of opinion, frustrated because of his economic position and unhappy about his accomplishments. The physician of the old school was as shrewd in his genius for character reading as in his flare for diagnostic intuition. Tomorrow, under controlled medicine, the physician will be a frustrated clerk, his scientific interest flattened under the dead weight of government regulation. From the vantage ground of the present moment, it appears that Medicine soon will be helplessly entangled in the tentacles of socialistic bureaucracy. For those who have anything to offer in opposition to this modern gravity, the time is now.

STUDIES ON GASTRITIS AND ULCER IN A NEW ALEXIS ST MARTIN

THE article by Wolf and Wolff in this issue is particularly helpful at this time, when a number of gastroscopists and others are puzzled over what interpretation to place on some of the changes they see in the gastric mucosa. At the last meeting of the American Gastro-Enterological Association and the American Gastroscopic Club, there was some difference of opinion about the nature of what has been called gastritis. All felt that there is no question about the fact that some mucous membranes are atrophic, but some doubted if this atrophy is produced or accompanied by inflammatory changes. They were not satisfied to call it *gastritis*, granting that we use the genitive ending "itis" in the usual way, meaning inflammation. Curiously, long ago physicians fell into the habit of leaving off the word inflammation and saying only "of the appendix" or "of the nerve" until now we all assume that "itis" is Latin for inflammation.

A good way of getting answers to some of the problems that have so puzzled the gastroscopists is to keep watching the mucosa hour after hour and day after day through a gastrostomy opening such as was so useful years ago to Beaumont in his studies, and this is what Wolf and Wolff have done. Observing the interior of the stomach of a man with a gastric fistula, they have come to the conclusion that Ruffin is right and that the gastric mucosa can be stretched until it presents the appearance of atrophic "gastritis." They found that now and then what looks like gastritis will appear temporarily in a normal stomach. They found that even what looks like severe hypertrophic gastritis can be produced suddenly by the gastric hyperemia and congestion that are sometimes associated with psychic disturbances. Later, within an hour or two the much swollen rugae became normal again. Obviously the swelling could not have been due to any inflammatory process. Interestingly, this hyperemia of

the gastric mucosa was associated with abdominal discomfort and even pain

A slight trauma produced by a blow with the tip of a glass rod caused a small area to become blanched and depressed for a few seconds. Several important observations were made showing how protective to the mucosa is the tough layer of mucus which normally adheres to it. This layer is sufficiently alkaline to maintain the surface of the gastric mucosa in a fairly neutral environment. The presence of hydrochloric acid tends to accelerate the output of this mucus. Remarkable was the observation that the gastric mucosa with its protective mucus is more resistant to strong irritants and corrosive agents than is the skin.

Interesting was the discovery that small hemorrhagic lesions in the mucosa caused a sharp acceleration of the secretion of acid and a concomitant hyperemia of the whole gastric mucosa. For years men have wondered if the hyperacidity seen with duodenal ulcer

was due to the ulcer or the cause of it. Wolf and Wolff felt their observation can now explain "the persistent hyperacidity regularly encountered in persons suffering with gastritis and peptic ulcer." The trouble with this argument is that careful statistical studies by Vanzant and her co-workers showed that with gastric ulcer there is, on the average, a decided lowering of gastric acidity. It is only duodenal ulcer which is associated with hyperacidity.

Wolf and Wolff were able in four days to produce a typical chronic peptic ulcer by exposing a small area of gastric mucosa continuously to the action of gastric juice. As soon as they decided to cure it, they covered it with a protective coating of petrolatum, and it healed in three days.

Wolf and Wolff are to be congratulated for having used to such good purpose another Alexis St. Martin. It is to be hoped that other cases will be used for such studies as opportunity offers.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

SCHATZKI R AND HAWES L E
The Roentgenological Appearance of Extramucosal Tumors of the Esophagus Am J Roent Rad Therapy, 48 1 July, 1942

Six cases of intramural tumors of the esophagus are reported. In three, 2 cysts and 1 neurofibroma, the diagnosis was confirmed. The authors attempt to establish a basic roentgen picture of intra and extra mucosal lesions, and point out that a definite histological diagnosis of intramural lesions is not possible. Of the 6 cases, there were several roentgenologic features in common. In the profile view there is an abrupt sharp angle where the edge of the tumor meets the uninvolved esophageal wall. In the en face view the lesions were sharply outlined in the relief picture. There was no obstruction to the passage of barium. In the large intramural tumors the esophagus was narrowed in one diameter, while being stretched and widened by the tumor in the opposite diameter, resulting in a slit-like lumen. In the en face view this flattened lumen showed barium irregularly distributed producing a "smear effect." Extramucosal tumors are often demonstrable as large soft tissue masses outside the barium cast. The authors point out that mucosal tumors are less apt to have such a

visible soft tissue mass—Maurice Feldman

STOMACH

BARLOW, D. *Treatment of Cardiospasm by the Heller Type of Operation* Brit J Surg, 29 415 April, 1942

The weight of evidence seems to point to two main primary conclusions with regard to cardiospasm, namely: 1. The disease is due to a disordered neuromuscular mechanism at or below the level of the diaphragm. The exact nature of this disorder is uncertain, but seems to be a condition of spasm than incoordination of the peristaltic wave. 2. There is reason to believe that the lesion is congenital in origin. In addition, two important secondary considerations are the complications which tend to follow, in varying degrees of severity, as a direct result of the primary obstruction: (1) Esophagitis, (2) Lengthening and sagging of the esophagus.

The operation is performed from the abdomen. The stomach is pulled down, the esophagus is freed. By blunt dissection of the longitudinal muscle anteriorly and extremely careful cutting through of the thin circular fibres, the esophageal mucosa appears at the bottom and bulges outwards. On its surface are one or two little submucous vessels which require ligation and division. The incision

should extend at least 2 inches on the esophagus and 1½ inches on the stomach. The vast majority of patients operated upon in this way showed a rapid and lasting functional improvement. Occasionally there was a slight tendency to regurgitation when lying flat in bed because of the persistently open cardia, but this was easily stopped by giving the patient an extra pillow. Although swallowing remains normal, the radiological examination may seem disappointing—Franz Lust.

TECOZ, R M. *Le Meteorisme Abdominal (The Abdominal Meteorism)* Gastro-Enterologia, 66 130, 1941

Following definition of the terms meteorism, tympanites and flatulence, the author enumerates the gases found in the gastro-intestinal tract. Nitrogen is present in a concentration about equal to that found in the air, and it occurs in aerophagy and in the intestinal canal of the infant; it is very slowly absorbed by the blood. Hydrogen occurs in the stomach of the breast fed infant and in the adult intestine, but not the stomach of the adult. Oxygen is found in the same concentration as in the air, whereas the percentage of carbon dioxide is much higher. The latter gas is absorbed very rapidly from the gastro-intestinal canal, but it also diffuses from the blood into the gastro-intestinal lumen with great velocity.

Clinical Experiments With Riboflavin, Inositol and Calcium Pantothenate

By

MARTIN G VORHAUS, M D, MICHAEL L GOMPERTZ, M D

and

AARON FEDER, M D

NEW YORK NEW YORK

DURING the past few years, the unsolved problems of nutritional deficiency states have been vigorously and successfully attacked by the biochemists and other investigators in related fields of science. New vitamins have been isolated, synthesized and administered to animals under varying experimental conditions. Although the preliminary reports of these studies seem confusing and at times contradictory, they are of great interest to the clinician. They challenge him to clarify and correlate this new knowledge and to evaluate its use in human deficiency states. It is the purpose of this report to describe such clinical investigations.

The therapeutic value of riboflavin in cases of cheilitis led us to study its effect in the treatment of decubitus with ulceration (7). Cases were accepted irrespective of the severity of the associated conditions. No case showing any clinical improvement on ordinary ward care was included in this series. Six cases are described in detail of which three were controlled rigidly. In these three cases no other vitamin supplement was given and no local treatment of the ulcer was permitted. In the other three cases the original disease required additional treatment which may be interpreted as having had some influence upon the decubitus. This additional treatment is described in detail.

CASE REPORTS

Case 1 S G, white male, aged 69, diagnosis—operable carcinoma of the sigmoid. Palliative transverse colostomy was performed on 1-9-41 and shortly thereafter a decubital ulceration directly over the sacrum was noted. The ulcer progressed steadily and on 1-22-41 measured 6.4 x 5.2 cms. The base was pale and unhealthy but the surrounding tissues seemed normal. The usual oral dose of 5 mgms of riboflavin was started at that time and continued daily thereafter. After four days of therapy the ulcer measured 5.7 x 3/4 cm and from then on continued improvement was seen, until on 2-19-41 (after 28 days of riboflavin therapy), the ulcer was completely healed. Three days later the patient was transferred to another hospital with no evidence of the previous sacral ulcer.

Case 2 A J, white female, aged 66, diagnosis—arteriosclerotic heart disease with decompensation, bundle branch block. Admitted 4-22-40. Decubital ulcers which became progressively worse were observed on each buttock. On 5-3-40 an ulceration measuring 2.5 x 1/2 cm was noted on the left buttock, and on the right buttock a smaller ulcer measuring 1.2 x 0.5 cm. On this day the daily oral dose of 5 mgms of riboflavin was begun. In three days beginning improvement was noted and by 5-8-40 (five days later) the left buttock ulcer measured only 1 cm in length and the right ulcer was almost healed. Gradual healing

continued until by 5-24-40, after three weeks of treatment, both ulcers were entirely healed and the skin of the buttocks appeared normal. This patient was observed until discharge on 6-2-40 and no evidence of the previous decubitus was noted.

Case 3 M R, white male, aged 60, diagnosis—arteriosclerotic gangrene of left lower extremity. Enormous decubital ulceration, shaped like an inverted triangle and involving about one-third of lower back was seen. Skin and subcutaneous tissue were missing over entire ulcerated area which varied in depth from one to three cms. Cheilitis at angles of the lips and outer canthi of both eyes were noted. On 4-8-40, nine days after admission, 5 mgms of riboflavin daily were given orally. Patient was under observation until death on 4-15-40. During these seven days the purulent discharge from the ulcer ceased. Necrosis diminished and small areas of granulation were observed. At the time of death the ulcer was found to be reduced more than one-third in area and the cheilitis of the lips and canthi of the eyes had disappeared.

Case 4 J C, white male, aged 44, diagnosis—thrombophlebitis of inferior vena cava with marked brawny induration of entire body below the costal margins complicated by suppuration in left thigh, probably secondary to the deep thrombophlebitis. On 2-24-40 beginning bed sore in sacral region noted. On 3-5-40 incision and drainage of abscess in left thigh. Progressive development of bed sore which became larger and deeper. On 3-20-40 this round ulcer over the sacrum measured 2.25 cms in diameter, its edge was beveled and its base appeared unhealthy. Five mgms of riboflavin by mouth started and continued daily. Ferrous sulfate and a whole B complex preparation were also given. In three days the ulcer began to improve. On 3-25-40 it had decreased to 1.75 cms, on 3-29-40 further decrease to 1 cm was noted. On 4-2-40 (thirteen days later) the ulcer was completely healed. At the time of the patient's discharge from the hospital (4-23-40) the sacral area appeared healthy and had remained free of ulceration.

Case 5 G S, white female, aged 58, diagnosis—oblique fracture of left femur. Admitted 4-12-40. On 4-30-40 pressure erosion was first noted in sacral region and over left lateral epicondylar region of the thigh. During the next ten days these lesions became progressively worse. At that time the sacral lesion measured 4 x 2 cms and the ulcer over the left thigh 3 x 2 cms. The surrounding skin was healthy. The daily oral administration of 5 mgms of riboflavin was started on 5-10-40. From 5-10-40 to 5-13-40 one tablet of Brewer's yeast was given three times a day by error but was discontinued on the latter date. During the period of riboflavin administration, estrone, which had been given for some time, was continued. By 5-17-40 the sacral ulcer was almost entirely healed and the thigh ulcer was reduced to a size of 2.5 x 1.3 cms. Seven days later (5-24-40) the ulcer of the thigh was completely healed. Riboflavin was reduced to 2 mgms daily. This patient was observed until discharge on 7-30-40 and the skin in the affected areas remained healthy.

*Read before the American Gastro-Enterological Association at Atlantic City on June 9, 1942.
From the Medical Service of the Hospital for Joint Diseases.
The Inositol and the Calcium Pantothenate were supplied by the Abbott Laboratories.

Case 6 S C, white male, aged 15, diagnosis—congestive heart disease with circulatory collapse, pulmonary edema followed by pneumonia, interlobar pulmonary effusion and thoracentesis. Admitted 11-21-40. On 12-6-40 an area of gangrene was noted over the sacrum. On 12-11-40 the decubital ulcer measured 5.1 x 3.2 cms. Its central portion had a depth of 2 cms and the base of the ulcer at this portion was covered with foul-smelling necrotic tissue. The oral administration of 5 mgms of riboflavin was begun on 12-11-40 and continued daily thereafter. Six days later this patient was placed on a high vitamin, high calorie diet. In six days the foul center slough had become clean and by 12-19-40 (eight days later), the ulcer had decreased to 3 x 3.2 cms in size. On 12-20-40 sulfathiazole 0.5 G t i d was given for two weeks, and on 1-11-41 a transfusion of 250 cc was also given. By 1-15-40 the ulcer measured 1.25 cms in diameter and tissue loss was only superficial. Improvement continued, with complete healing of the lesion noted on 2-3-41 (seven weeks later), but sulfathiazole had been resumed on 2-2-41 in doses of 1 G Q 4h and was continued until 2-9-41. The following day he received an additional transfusion of 500 cc. This patient remained under observation until discharge from the hospital on 3-6-41, at which time the sacral area was healthy.

DISCUSSION

Six cases of decubital ulceration were treated by the daily oral administration of 5 mgms of riboflavin. Five of these cases showed complete healing of the ulcers in from seven to thirty-four days of riboflavin therapy. The sixth case died after seven days of treatment with riboflavin and at death the decubital ulceration was reduced in size and showed evidence of healing.

Since improvement in these six cases was noted within a few days after the institution of riboflavin, it would seem likely that the healing of these ulcers was due to the vitamin therapy. The continued and progressive development of these lesions up to the day on which riboflavin was first given should be emphasized. It is unlikely that the improvement in the local lesion could have been an expression of a generalized systemic improvement. On the contrary the general condition of Case 2 grew progressively worse and ended in death, Case 5 had an inoperable carcinoma of the sigmoid.

It is not to be inferred from these observations that decubital ulceration is a clinical manifestation of ariboflavinosis nor are these results to be interpreted as evidence that riboflavin is a specific in the treatment of bed sores. It is interesting to recall that early in our clinical experiments with riboflavin many observers believed that cheilitis was a clinical state characteristic of riboflavin deficiency. Subsequent studies have been reported in which the administration of pyridoxine in cases of cheilitis has been followed by the disappearance of these lesions. Furthermore, cases of cheilitis which have been resistant to riboflavin therapy have shown complete healing when pyridoxine was given (5).

It is extremely likely that other members of the B complex as well as riboflavin may exert a favorable effect upon decubital ulceration. Quite probably the addition of the entire B complex to the riboflavin administered might have resulted in a more rapid improvement in the local lesions of these six cases. Such clinical possibilities are in keeping with our increasing knowledge of vitamin therapy.

Bed sores are generally slow-healing indolent lesions and their rapid response to riboflavin therapy

gives rise to speculation as to the mechanism involved. Riboflavin is an essential factor in nutrition and is of great importance to the oxidation enzymes of the body. It is believed to be a basic constituent of the xanthine oxidase and thus establishes a closer link between vitamins and tissue enzymes (1).

The lesions of the skin and subcutaneous tissue in cheilitis have a parallel in miniature to the tissue changes seen at times in decubital ulceration, and the clinical response in both of these lesions to the administration of riboflavin serves to emphasize this parallelism. Further speculation seems to relate the various members of the B complex to tissues of original ectodermal origin, thiamin to nerve tissue, nicotinic acid to skin and mucous membrane, riboflavin and probably pyridoxine to skin and subcutaneous tissue. Now that inositol and pantothenic acid are available it seems logical to conjecture whether these two newer members of the B complex are not also possessed of an influence on epithelium or similar tissues.

Although inositol was first isolated in 1850 (19), it was not believed to have an essential role in nutrition until Woolley in 1940 identified it as the mouse anti alopecia factor (13). The alopecia produced in mice by a deficient diet was not influenced by biotin or p-aminobenzoic acid. This diet contained adequate pantothenic acid, in addition to other members of the B complex. However when inositol or some of its derivatives were added to the diet the alopecia disappeared (12).

Pure inositol was made available to us for study and it seemed logical to explore its possible value in diseases of the skin and hair. On the basis of present concepts the daily adult requirement of the human being is about one gram. Several volunteers were asked to take this amount daily and no untoward effects were observed.

In a recent communication, studies on animals suggested that inositol appears to stimulate intestinal peristalsis (6). This question has been followed clinically in twenty patients taking from one to two grams of inositol daily. In not one of these cases was any change in the normal bowel habits noted, even though many of them had mild to moderate constipation.

Gavin and McHenry found a similarity between the action of inositol and lipocaine in preventing the "biotin" type of fatty liver (3). With this in mind inositol was administered to a 58 year-old female diabetic with a blood cholesterol of 398 mgms. This patient also had a bilateral symmetrical thickened eruption of the lower extremities and back. After the patient had received 2 grams of inositol daily for three weeks the eruption had cleared. The cholesterol was 313 mgms several days after discontinuing the inositol. Further studies are in progress and will be reported.

Cases of alopecia have been selected for study and daily doses of from one to two grams of inositol have been administered to these patients for several weeks and in some instances for over two months. Definite conclusions are not possible at this time, but on the basis of our early observations there are not sufficient changes to indicate that inositol is the human anti alopecia factor.

With the aid of our associates in the field of dermatology a systematic survey is at present being made of

the possible value of inositol in a variety of skin diseases hitherto resistant to treatment. These detailed studies will be reported later, but our preliminary observations seem to indicate that inositol may have a value in some skin diseases. Two examples of such a response are described in detail.

An 84 year-old female suffering from an extensive generalized pruritic eruption with thickening and desquamation was treated by a dermatologist for four months. The eruption failed to respond to a variety of local medication, X-ray and Vitamin A orally. She volunteered for inositol therapy. After all other treatment had been stopped for three weeks and no change in the eruption had occurred, she was given 0.5 gram tablets of inositol orally, twice a day. In ten days there was a lessening of the pruritus, in two weeks a modification of the eruption, and at the end of five weeks the eruption had almost entirely disappeared.

A 51 year-old male diabetic had a pruritic thick scaly symmetrical eruption involving both ankles and the inner aspect of both feet. Smears and cultures for fungi were negative, and treatment for two years by various dermatologists had not modified the eruption. He volunteered for inositol and was placed on one gram daily by mouth. Within two weeks there was a reduction in the amount of the eruption and at the end of nine weeks the eruption had almost entirely disappeared. Medication was then discontinued in order to evaluate clearly the effect of the inositol upon the eruption. Within two weeks the eruption again was manifest and at the end of two months had developed to its original extent and severity. Inositol has been resumed recently with its original beneficial effect.

Since the chemical identification of pantothenic acid and its synthesis two years ago (9, 11, 10), it has been confirmed over and over again that pantothenic acid is one of the factors primarily responsible for the prevention of nutritional achromotrichia in animals (8, 2, 4).

Recent studies in animal experimentation indicate that inositol and calcium pantothenate exert a definite influence on tissues of ectodermal origin. Woolley has emphasized the relationship between inositol and pantothenic acid, since the quantity of pantothenic acid fed influenced his animal cases of alopecia (14, 15). In some instances, with inclusion of large amounts of calcium pantothenate in the diet, no alopecia developed, even though there was a marked absence of inositol in the rations fed. The explanation for this tends to emphasize more emphatically the interrelationship of vitamins of the B complex. It has recently been reported that mice are able to synthesize inositol, if sufficiently high levels of pantothenic acid are fed, by means of intestinal micro-organisms (17). These reports are so very recent that they are mentioned here only to show the trend in animal experimentation. Thus far, no human clinical research in this direction has been reported. Woolley has shown that mice fed on a low pantothenic acid diet developed signs of inositol deficiency. When these animals are given further supplements of inositol by mouth then signs of inositol deficiency continue unabated. Woolley raises the question as to whether there is interference of inositol absorption or destruction of the ingested inositol. In this connection Martin has varied these experiments in an attempt to answer this question. When his mice on a low pantothenic acid diet de-

veloped signs of inositol deficiency he injected inositol intramuscularly and observed the disappearance of the signs of inositol deprivation (18).

Calcium pantothenate was made available for study. One hundred mgms of pantothenic acid were given twice a week by intramuscular injections to three volunteers for six weeks. No effect upon the gray hair present was noted. In one case of alopecia totalis (a 54 year-old white male) one gram of inositol was given daily by mouth and 100 mgms of calcium pantothenate were injected intramuscularly twice a week for six weeks. At the end of this test period no change was noted and the experiment was discontinued.

A 45 year-old white male with alopecia areata for three years volunteered for treatment. Before treatment white hair had regrown in some of the areas of alopecia. 655 mgms of calcium pantothenate were given by intramuscular injection during ten weeks in varying amounts, and at the end of this time there was an unmistakable new growth of black hair in a central white streak. In the next two months 950 mgms more of calcium pantothenate were given. At the end of that time no new growth was noted, although the previous old black hair was about one inch long. The treatment was stopped for two months and at the end of that time there was no change in the hair. In the next two months 42 grams of inositol were given in divided doses by mouth, and no change was noted. Then calcium pantothenate was again given by injection in doses of 500 mgms intramuscularly twice a week. Twelve injections (a total of 6000 mgms) were given and a slight new growth of black hair was observed. During all this time no pigmentation was noted in the areas of white hair present in this patient. Further studies are in progress and will be reported.

DISCUSSION

Although inositol has been known for many years and used extensively in animal experiments by Woolley in the past two years, no reports of its use in humans have appeared. Since we have reason to believe that this is the first time pure inositol has been given to human subjects, observations were made on doses of inositol that approached physiologic amounts. From analyses of the human diet it is assumed that the daily requirement of inositol is about one gram. All our observations were made in cases receiving one or two grams daily and the inositol was given in the form of 0.5 G tablets in divided doses, irrespective of meals.

Our preliminary observations indicate that in these doses there is no apparent harmful effect of inositol in healthy subjects. Furthermore, the bowel habits of our patients were not modified by this amount of inositol and therefore in these doses there is no clinical confirmation of the previous report that inositol stimulates intestinal peristalsis.

The results of animal experiments with inositol present two outstanding facts—firstly, that the signs of inositol deficiency in animals seem to be mainly changes in the skin and hair and, secondly, that inositol is used by animals to make more complex tissue substances. One such substance has been identified as phosphatide, found in the brain and nerve tissue, it appears to be a combination in some complex

form of inositol and phosphates (16) This combination is lipid soluble in contradistinction to the water soluble compound in muscle which is made up of inositol and other as yet unidentified substances (18)

After we were convinced that inositol has no harmful effect in our doses we administered this vitamin to a number of patients with alopecia both total and regional and to a number of patients with chronic bilateral skin eruptions of unknown etiology hitherto resistant to all forms of therapy In the cases of alopecia we did not observe any regrowth of hair In the cases with various skin diseases we have noted both negative and positive results Several examples of rapid improvement in chronic eruptions following the administration of inositol are detailed Our experience is still too recent to permit definite statements that inositol is or is not of benefit to any particular skin disease However, it offers a new approach to the problems of dermatology and it is hoped that continued and extensive clinical trials will be made by the workers in this field

There has been much comment as to the value of calcium pantothenate as an anti-gray hair factor In our hands this has not been the case Even though we used huge doses, from 100 to 500 mgms per injection, we have only rarely noted any response in the hair When response was apparent it occurred as a new growth of pigmented hair but no change in the existing gray hair was seen

CONCLUSIONS

Riboflavin appears to be of value in the treatment of decubital ulceration Following its administration the bed sores show rapid healing The combined use of riboflavin and the entire B complex may be of even greater value in decubitus

Inositol in doses of from one to two grams by mouth has no apparent harmful effect In alopecia no beneficial results were noted Rapid response in a variety of skin diseases following inositol administration were observed It is hoped that the dermatologists will study this vitamin and clarify its field of usefulness

Calcium pantothenate seems to have little value as a human anti-gray hair factor

We wish to thank Dr A J Beller, Dr Milton Bodenheimer, Dr Morris Dinnerstein, Dr A A Epstein and Dr S Jahss for permission to use their cases

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DISCUSSION

DR HARRY SHAY (Philadelphia) Mr President Ladies and Gentlemen I think this contribution of Dr Vorhaus extremely important We are beginning to recognize the importance of some of the newer members of the B group, in animal and in human metabolism We have had some experience with inositol in the human being, not in relation to skin changes, but were tempted to try inositol for its effect on fat metabolism based on the work of McHenry and his group at Toronto

McHenry was able to produce cholesterol fatty changes in the liver in Vitamin B deficient animals given Biotin. He was able to prevent and cure these fatty livers with lipocain and subsequently was able to do the same thing with inositol

On the basis of these observations, we were prompted to study the effect of inositol in the diabetic, particularly in the diabetic with enlarged liver Not knowing the required dose for the human being, we calculated our dosage on the basis of McHenry's results He was able to produce beneficial results in his rats with a 5-milligram dose and, considering the average rat as a half pound, we decided upon the use of 12 grams a day for the average patient

We administered 12 grams per day to humans for a considerable period, without any ill effects, but, unfortunately, without being able to produce changes in the blood cholesterol levels or in the size of the liver

The Oral Use of the Amino-Acids of Hydrolyzed Casein (Amigen) in Surgical Patients

By

ROBERT ELMAN, M D
ST LOUIS MISSOURI

FROM time to time "predigested" protein has been fed to a variety of patients and indeed preparations have been described which were administered per rectum These attempts to spare protein digestion, aroused very little interest probably because very little was known of protein and amino-acid metabolism That proteins are normally absorbed from the intes-

tine as amino-acids is now generally agreed The problem of saving the body the need for protein digestion reduces itself to the administration of an appropriate mixture of amino-acids, particularly those which are now known as essential Inasmuch as mixtures of these building stones of protein in the pure form are at present prohibitively expensive, it is necessary to obtain them by the appropriate hydrolysis of complete proteins Such a preparation has been available for several years and we have used it

*From Washington University Department of Surgery and Barnes Hospital St. Louis Missouri
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extensively in surgical patients unable to take nourishment by mouth as a means of intravenous feeding with good evidence of utilization and clinical benefit (1, 2) The present brief and really preliminary report, concerns the use of this same hydrolyzed protein orally, or by enterostomy tube in a variety of surgical patients

PRESENT OBSERVATIONS

The mixture of amino-acids used is prepared by the hydrolysis of casein and is called Amigen. It contains all of the amino-acids present in casein although a part (about 30%) is in the form of smaller polypeptides. When given by mouth or through an enterostomy tube, it is simply dissolved in water, usually as a 10% solution, and given with equal or larger amounts of dextrose. Vitamins and salts are added, and fats, too, if desired.

Our observations may be arbitrarily divided into three groups

1 Patients in whom whole protein by mouth

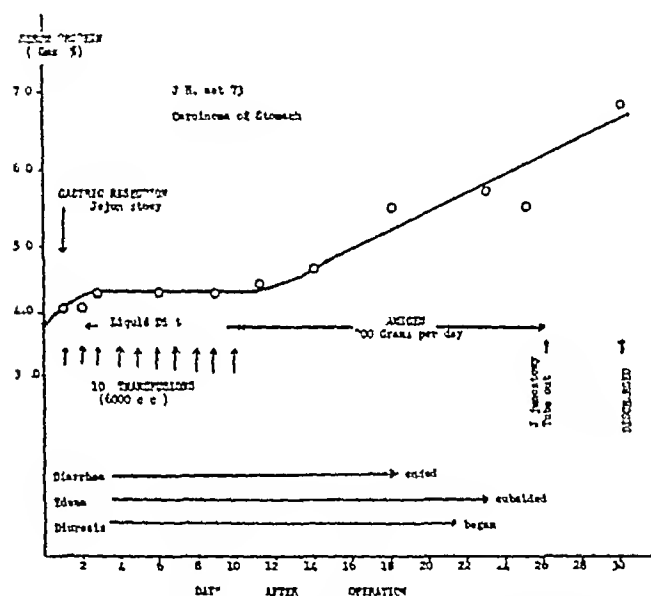


Fig. 1. Note the prompt return of the serum protein toward normal after the start of Amigen feedings. The serum protein content of the 6000 cc of blood is less than 400 grams, illustrating the difficulty in supplying large amounts of protein nourishment in this way.

seemed to be inadequately digested, due, presumably, to nutritional edema of the gastro-intestinal tract. Hypoproteinemia was severe in all of these patients and external edema was often visible. Persistent diarrhea indicated clearly the failure of normal digestion and absorption. The malnutrition in many of these patients was due to an esophageal obstruction and a gastrostomy had been performed as in the following case.

Case 1 J H L (B H 92628) An 85 year-old male had a complete esophageal obstruction due to carcinoma. On October 6, 1941, a gastrostomy was performed and tube feeding of liquids (i.e., milk, eggs, etc.) was started five days later. Within three days diarrhea began and persisted for five days. Feedings with 100 grams of Amigen daily, and dextrose were then substituted. The diarrhea disappeared promptly and the patient was discharged on October 28, 1941, much improved.

2 Patients who could be fed only through a tube emptying directly into the jejunum. In some of these

patients the tube was a long nasal catheter placed into the jejunum at the time of operation, across the lumen of the stomach past the anastomosis just before the gastro-enterostomy was completed. In a recent case, for example, I was able to introduce 100 grams of Amigen per day for three days immediately after operation directly into the jejunum through the nasal catheter which I had led down into the intestine at the time of the gastro-enterostomy, although nitrogen balance was achieved and the abdomen remained scaphoid, the patient preferred the intravenous route, and I had to remove the tube and give him the same amount of glucose and Amigen per vein. In other patients a jejunostomy was performed directly, the tube leading through the abdominal wall to the outside.

The following case is a striking one, the details of which I am indebted to Dr I C Middleman who operated on the patient and furnished the detailed data which is presented in the following chart.

Case 2 J H, a 73 year-old male, was operated upon at the Jewish Hospital on June 24, 1940, and a carcinoma of the stomach was found. A gastric resection and jejunostomy was performed. Two days later liquid feedings were started but diarrhea promptly began. There was a severe hypoproteinemia and tissue edema which was scarcely affected by 6000 cc of whole blood given over a period of a week. Soon after, the daily feedings were changed to 200 grams of Amigen plus glucose and adequate vitamins. The patient began to improve, the serum protein began to go up, the edema disappeared and the patient left the hospital very much improved.

3 The patients in whom especially large amounts of protein nourishment are needed in order to correct nutritional deficiency as rapidly as possible. In severely depleted patients all protein tissue is obviously affected as well as the serum protein. As pointed out in experimental studies from our laboratory (3) it is probable that tissue proteins must be supplied with adequate protein if the hypoproteinemia is also to be corrected. According to this hypothesis, it was calculated that as much as 2000 grams of protein may be needed to restore a moderately depleted serum protein to normal.

The upper level of protein intake, even in normal individuals, is usually placed at about 150 to 200 grams. By sparing the need for protein digestion we have been able to give twice this amount. Adequate carbohydrate in the form of dextrose, can similarly be given without the need for any digestion. What the maximum amount of protein the body can assimilate in 24 hours in this way is as yet unknown. There is here an obvious time advantage in preparing a patient for operation, e.g., the difference between two weeks and three or four days. In the following patient we did raise the intake to 400 grams per day of hydrolyzed casein but it seemed to provoke diarrhea at this level. The cause was held to be sure of because he had very extensive carcinoma of the esophagus and was receiving daily treatments with the X-ray. Nevertheless, he retained and utilized most of the large nitrogen intake.

Case 3 P K (B H 94138) A 54 year-old male with an extensive carcinoma of the cervical esophagus was operated on December 17, 1941, and a gastrostomy performed. Beginning about a week afterward he was started on Amigen with glucose salts and vitamins added. The

amount was at first 100 grams per day but was increased gradually to 400 grams per day. He was always in positive nitrogen balance and retained as much as 26 grams of nitrogen a day. It was hard to evaluate his general condition because of the extensions of the cancer and the intensive radiotherapy. He was discharged somewhat improved, one month after the operation.

COMMENT

The present observations permit but limited inference because further and more complete studies are obviously required. These studies should include careful nitrogen balance studies as well as measurements of serum protein concentrations, preferably with plasma volume determinations. Nevertheless the advantages of sparing protein digestion by the administration of large amounts of a nearly completely hydrolyzed protein seem great enough to justify further study. Besides the surgical patients mentioned above, other patients would probably also be benefited by such treatment, e.g., patients with hypermobility of the gastro-intestinal tract due to many other conditions, and those with pancreatic or other enzymic deficiency where protein is not normally digested and absorbed.

SUMMARY

The amino-acids of hydrolyzed casein (Amigen) have been administered directly into the gastro-intestinal tract in several types of surgical patients in order to spare the need for protein digestion. Absorption and utilization occurs under circumstances when whole protein is ineffective. The use of Amigen also seems to permit the assimilation of much larger daily amounts of protein nourishment than seems possible when whole protein is given.

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DISCUSSION

DR GRAY (Chicago) If the liver is the key organ in the synthesis of protein when amino acids are administered, I don't believe that the response will be as good in the presence of advanced or moderately advanced liver disease.

Apparently amino-acids are synthesized into some intermediate form of protein in the liver, by electrophoretic analysis we can see the albumin in the diseased liver is less likely to be synthesized while the larger molecular weight is more easily synthesized, when the prosynthesis of proteins is less marked, the administration of the amino-acids will be less marked, and in those cases, perhaps, I believe that the transfusions and whole protein administration will be necessary.

DR ROBERT ELMAN (St Louis) (closing the discussion) The point brought up by Dr Gray, is very important and illustrated by a recent case of acute yellow atrophy following pregnancy. I was asked to see this case in consultation. I felt, of course, that amino-acids were contraindicated. However, we gave the patient 1000 cc of plasmas per day for a week, with a most dramatic response in the clinical course of the patient, I believe this was our only case of post-partum acute yellow atrophy which has recovered.

I would like to make a further comment about a number of different hydrolysates or mixtures of amino-acids which are available for use, and to suggest that three criteria be established for these hydrolysates. First, that we know exactly what protein has been used as a source of material, second, what method of hydrolysis has been used because various methods will destroy some of the essential amino-acids, third, that these hydrolysates be subjected to three tests of biological activity: (a) growth curves—with the hydrolysate as the only source of nitrogen, (b) nitrogen balance studies, and (c) serum protein regeneration studies.

The Relationship Between Roentgenographic Abnormalities of the Gall Bladder and Constipation*

By

GRANT H. LAING, M.D., J. M. BEAZELL, M.D.

and

ANDREW C. IVY, M.D.

CHICAGO, ILLINOIS

THIS study was undertaken since several reports in the literature indicate that a disturbance of the motor function of the colon may affect the evacuation of the gall bladder. Boyden and Birch reported that stimulation of the cecum in cats inhibited the evacuation of the gall bladder. Goldman and Ivy found that stimulation or distention of the dog's colon definitely increased the tone of the sphincter of Oddi. Lahey and Jordan observed improvement of gall bladder visualization in 44 out of 65 patients after their irritable colons had been treated for a short period. In autopsy records Kocour found that the incidence of

cholecystopathy was doubled in subjects with diverticulosis. In view of these reports it was believed that further observations on the human should be made. We were also interested in ascertaining whether any evidence might be obtained which indicated that gall bladder stasis predisposed to stones.

The records of 372 consecutive patients who had been subjected to a complete gastro-intestinal roentgenographic examination have been analyzed in regard to the relation of "constipation" to, first, abnormal visualization, second, delayed evacuation of the gall bladder, and third, to the presence of gall stones. For the purpose of this study, "constipation" was accepted as being present at the time of the first gall bladder visualization if the patient reported the

*From the Department of Physiology and Pharmacology, Northwestern University Medical School, and the Department of Clinical Research, St. Luke's Hospital, Chicago, Ill.

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frequent use of cathartics and the belief that a cathartic was required to produce a stool and prevent stasis. Obviously most of the patients had an irritable bowel which readily responded to ordinary management. In addition to the complaint of "constipation," the patients emphasized symptoms referable to the biliary tract of sufficient import to warrant cholecystography.

Where the gall bladder failed to visualize or visualized poorly it has been classified under the heading "abnormal visualization." Stones have been diagnosed only where defects in the shadow have clearly established their presence, and finally it has been considered that the gall bladder exhibited delayed evacuation when it retained dye 2 hours after a fatty meal. Admittedly, neither failure of visualization nor incomplete dye evacuation constitute unequivocal evidence of gall bladder dysfunction. Yet Boyden, who has made the most serious study of the rate of evacuation of the gall bladder in normal subjects, has reached the following conclusions. He found that from 60 to 80% of the dye was evacuated in 40 minutes, and that 95% was evacuated in one hour and 40 minutes. This has been questioned by some roentgenologists, but their criteria of normality is based chiefly on observations in patients presenting gastro-intestinal symptoms, rather than on observations in normal individuals.

Of the 372 patients studied, 91, or 24.4% gave a history of constipation as described above. (Slide, please). The data showing the incidence of gall bladder abnormalities both in the constipated and non-constipated groups are assembled on the slide. It will be seen that the frequency of abnormal visualization and of stones does not differ significantly between the two groups. With respect to incomplete dye evacuation, however, the difference between the two groups is quite marked. That this difference is real has been established by statistical analysis, using the 4-fold table and applying Fisher's rule. When these values were subjected to further analysis it was found that in the case of both sexes the trend toward a correlation between constipation and incomplete gall bladder evacuation was present in all age groups.

Our data established that there is a relationship between disturbed motor activity of the colon and delayed emptying of the gall bladder. In the presence of a disturbed colon the gall bladder tends to empty slowly. Whether the incomplete emptying of the gall bladder predisposes to clear cut gall bladder disease cannot be stated with assurance. On the basis of theoretical considerations one would expect that a sluggish gall bladder would be more vulnerable to infection and more apt to lead to stone formation. An examination of our data, however, does not bear this out. Even though there was a clear-cut difference between the constipated and non-constipated groups with respect to gall bladder evacuation, there was no difference between the two groups with respect to the incidence of

stones. This offers presumptive evidence that gall bladder stasis alone does not predispose to stone formation. The fact that there was no correlation between the incidence of delayed evacuation and the incidence of abnormal visualization suggests further that gall bladder stasis alone does not predispose to infection. This conclusion is based on the assumption that a gall bladder that fails to concentrate dye probably is or has been, the site of infection. Summarizing our data demonstrate that constipation and sluggish gall bladder evacuation are related. Our data further indicate that gall bladder stasis alone is not a predisposing factor in the production of either gall stones or gall bladder infection.

DISCUSSION

DR SARA M JORDAN (Boston) Mr President and Ladies and Gentlemen I think this paper has great clinical importance for the following reasons.

First of all with regard to the word "constipation"—let us consider that for a few moments—Dr Laing definitely defined it as signifying the frequent use of laxatives and the implication of the frequent use of laxatives is that we very often have a picture of an irritable colon, a colon which is both spastic and dilated at times, abnormal dilatations, abnormal contractions, and in our experience this kind of colon does have its effect upon the gall bladder function.

Practically speaking, the observations here made can be related to both pre-operative diagnosis and post-operative treatment of gall bladder cases, in other words, the diagnosis of a poorly functioning gall bladder should, on the basis of these observations, and I think on the basis of many of our clinical observations never be made because a gall bladder on one observation fails to fill normally or fails to contract normally.

In our experience it is most important in such instances, if the dye cannot be given intravenously and repeated intravenously, to put the patient under observation, treat the abnormal contractions and abnormal dilatations in the colon or in the digestive tract generally, and then re-examine with a repeated oral cholecystogram, and in very many instances what was thought to be an abnormally functioning gall bladder proves to be a perfectly normal one.

Now, the corollary of that is that the troublesome cases which we used to have post-cholecystectomy, are now much better managed because we recognize that not only the gall bladder was at fault, even with stones, but the rest of the digestive tract, and particularly the colon, and treatment of the colon, avoiding as much as possible, spasm and abnormal dilatation, results in good results versus bad results after gall bladder operation in very many instances.

It is a most important observation and it is interesting to find that this experimental work has resulted in the same observations which we have been making clinically in these last few years.

DR GRANT H LAING (Chicago) (closing the discussion) I have nothing to add except to say we are in complete agreement with Dr Jordan as to the post-operative procedure.

Giardiasis With Unusual Clinical Findings

Preliminary Report

By

P B WELCH, M D
MIAMI FLORIDA

THE advent of atabrine as a specific treatment has made it possible to definitely establish giardiasis as a clinical entity and to more accurately identify and evaluate its symptoms and its findings physical, laboratory and X-ray

Using this response to atabrine therapy as a guide in 12 of 13 cases of giardiasis, it has been possible to show, (1) that the general symptoms in this small series have compared fairly accurately with those previously published by numerous observers (2) that radiologic evidence of motor or inflammatory changes in the pyloric or duodenal areas is fairly constant, and (3) that eosinophilia occurred in a relatively high proportion of cases (7 out of 12), and disappeared after one or more courses of atabrine therapy in all recorded cases except one. In this instance there was definite clinical improvement, the giardia disappeared from the stool, but the eosinophile count continued at the same level.

The general symptoms encountered and their response to treatment are listed in the order of their frequency in Table I. There was prompt symptomatic

TABLE I

General symptoms before and after atabrine therapy

General Symptoms	No. Cases Before	No. Cases After
Abdominal pain	11	3
Abdominal distress	9	2
Abdominal tenderness	8	2
Emotional instability depression nervousness	8	2
Nausea	6	1
Diarrhea	6	0
Loss of weight	5	0
Constipation	4	2
Anorexia	4	0

relief in all but one, although in three instances it was necessary to repeat the course of atabrine before the stools became negative. Relief frequently began within 3 to 5 days after initiation of treatment and was usually very complete.

X-RAY

Fluoroscopic and radiologic studies were made in all thirteen cases and repeated in ten cases after treatment with atabrine. In all thirteen cases there occurred motor disturbances or other evidences of irritation in the duodenum, duodenal cap, pylorus or pre-

pyloric portion of the stomach. There has been only casual mention of these changes in the medical literature. Mary Spears (1) reported radiologic evidence of an irritable and spastic duodenum in 12 of a series of 24 cases. In the ten cases re-examined radiographically after therapy, all but three showed varying degrees of improvement. One of these had an active low grade cholecystitis and had previously shown giardia in all fractions of the duodeno-biliary drainage.

As shown in Table II, there were two cases of duo-

TABLE II
X-ray diagnoses

Diagnosis	No. Cases
Duodenitis	4
Duodenal irritability	3
Duodenal ulcer	2
Pyloric hypertrophy	2
Pylorospasm	2
Duodenal stasis	1
Cholecystitis	1
Procto-colitis, subacute	1

denal ulcer and two of pyloric hypertrophy. Giardiasis is not presumed to be the etiologic factor in these four cases. The two ulcer cases had been on ulcer management prior to the administration of atabrine. Their ulcer symptoms were controlled but the abdominal distress persisted and disappeared only after the atabrine therapy. One case of pyloric hypertrophy occurred in an adult, the other in a child who had been perfectly well until four months prior to coming under observation. Repeated X-rays had shown an intermittent pyloric stenosis with hypertrophy, associated with nausea, vomiting, diarrhea, repeatedly negative stool, abdominal pain and tenderness, and an eosinophilia of 3% to 10%. The appendix was suspected and removed without relief. Eventually further stool examinations revealed very large numbers of giardial trophozoites. Several courses of atabrine were required to clear up the infestation. Re-examination of the stomach several months later showed a normally functioning pylorus with a slightly elongated pyloric canal. It is probable that there pre-existed an asymptomatic congenital pyloric hypertrophy which was aggravated by the giardial infestations.

The almost constant association of radiologic evidence of motor or inflammatory changes in the pyloric and duodenal areas suggests that these findings may eventually be shown to be as characteristic of giardial

infestations as the changes seen in the duodenal aspirates

EOSINOPHILIA

A review of differential white counts in non-allergic individuals in this geographic area has shown an average eosinophile count of 0 to 2 per cent, therefore, counts of 4 per cent or more in this series have been considered an eosinophilia. This assumption has apparently been justified by the prompt drop in eosinophiles in all but one case recorded following the administration of one or more courses of atabrine. Whether or not atabrine would reduce the eosinophilia in conditions other than giardiasis is not known.

Eosinophile counts were recorded in 12 of 13 cases studied. Counts of 4 to 11 per cent were found in 7 (Table III). In six of these seven cases, counts were

TABLE III
Blood picture before and after atabrine

Before		After	
W B C	Eos %	W B C	Eos %
8 600	3 10	—	1
—	8 11	7 600	2
10 050	7	7 000	4 2
11 700	6	16 750	1
7 450	4	—	0
12 750	0	8 000	0
12 000	7	—	—
11 700	3	9 400	1
5 950	3	6 200	1
9 200	0	8 650	0
—	2	—	0
13 250	0	9 600	2

made after treatment with atabrine. In five the count dropped to normal, none being over 2%. In two other instances counts of 3% were encountered. Both of these dropped to 1% after treatment.

There was an apparent, though not conclusive relationship between the severity of the infestation and the degree of eosinophilia. The drop in the eosinophile count usually paralleled the clinical improvement. The drop in eosinophile count in two cases from 3% to 1% after treatment may or may not be significant.

The occurrence of eosinophilia has not been previously reported as a characteristic finding in giardiasis. In fact, Lyon and Swalm (2), in 1925, stated that "absence of noteworthy eosinophilia therefore seems to distinguish this infection from other forms of parasites." In 1935 MacPhee and Walker (3), in a very complete survey of the literature on giardiasis, stated, "All writers who have considered the question of giardiasis at all, agree that this infection is not accompanied by eosinophilia." These are formidable and authoritative statements.

In the literature since 1935, only two references to the occurrence of eosinophilia have been found. Hall (4) reported an eosinophilia in two out of four cases studied. Love and Tayloe (5) reported an eosinophilia of 5% in one of three cases reported.

It is difficult to reconcile these positive statements

of the absence of eosinophilia in giardial infestations with the finding in this series, of an incidence of 58%. It is still more difficult to explain the return to a normal eosinophile count after atabrine therapy.

It is possible, of course, that the occurrence of eosinophilia in such a small group as here reported may be an artefact, but the prompt fall of the eosinophilia after atabrine therapy mitigates against such a possibility.

It is necessary to reiterate that no definite conclusions should be drawn from this small series, but the possibility of eosinophilia being a characteristic finding in giardiasis must be considered and merits further investigation.

SUMMARY

Thirteen cases of giardiasis have been studied. The incidence and character of general symptoms has closely paralleled those previously reported. Radiologic evidence of motor or inflammatory changes in the duodenal or pyloric areas was observed in all cases. Eosinophilia was encountered in seven cases with return to normal after atabrine therapy in five. The eosinophilia usually paralleled the degree of infestation and symptomatic relief after treatment.

CONCLUSION

Atabrine therapy has made possible clarification of the symptoms and findings in giardial infestations. Further study may show that radiologic evidence of functional and inflammatory changes in the duodenal and pyloric areas is characteristic in giardiasis. The relatively high incidence of eosinophilia and its response to atabrine therapy in this series suggests that it may be characteristic of severe giardial infestations and should be provocative of further study.

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DISCUSSION

DR HOWARD R. HARTMAN (Rochester, Minn.) We have treated approximately seventy-five patients in the Mayo Clinic with atabrine, infected with giardiasis, and have had many more people in the clinic, and this was attributed to the fact that they were before 1937, when atabrine was first announced as a specific of the treatment of giardiasis.

In our series of patients we have had but one failure from one course of treatment and I should like to ask Dr. Welch what he meant by a "course of treatment." We use fifteen tablets, 1 gram each, taken three times a day.

It contributes to the radiographic evidence of deformity of the duodenum because the Giardia live in the duodenum, that is the Protozoa live there. We have found the Giardia has invaded the biliary system. In one recently reported case the bile was taken at the time of operation, cholecystostomy, and the Giardia were swarming in the bile. No one has ever yet demonstrated how it produces symptoms, whether it attaches to the duodenal wall or elaborates the toxin. It produces symptoms locally as well as quite irrelevant to the location of the parasite.

Unfortunately, we are one of the persons who failed to contribute to the knowledge of eosinophilia in giardiasis.

Perhaps this will be a lead in the future to more accurate study of the effect of this parasite

DR WALTER L PALMER (Chicago) Before Dr Hartman gets away, may I ask a question? I think he misspoke when he mentioned the dosage

DR HARTMAN A tenth of a gram

DR. PALMER You referred to failure after one course Did you ultimately cure that patient?

DR HARTMAN That patient was a most uncooperative individual He happened to be a man who traveled through the northern part of Mexico with a pack on his back, most illiterate, and I doubt very much if he ever took the medicine

DR. PALMER I should like to find out if there are any cases that cannot be cured if the treatment is persisted in

DR HARTMAN Ask Dr Welch

DR WILLIAM A SWALM (Philadelphia) Mr President, Ladies and Gentlemen In answer to Dr Palmer, I should like to mention that in New York, in the discussions of Dr Spear's paper, one New York physician said he failed to eradicate giardiasis by repeated doses of Atabrine.

I was interested in the problem of Atabrine and sent out five hundred questionnaires Probably some of you received these, concerning this eradication of the parasite, and I was very pleased to hear that some of the gentlemen had given it in over two hundred, even up to six hundred cases, and in the majority of those cases they all agreed that Atabrine was the drug of choice

Dr Morrison and I reported a smaller series, and we had over 90 per cent cures. I believe that if Atabrine does not eradicate the parasite on the first or even second course, a third course should be given, and I often do so. We give the same as Dr Hartman, a grain and a half three times a day for five days, and then stop, as you would with any of the arsenicals, and in a week or ten days, we repeat it. I always repeat it at least once in every case. Then we watch the duodenal aspirates and if it recurs within six months, we give it again, and to date all of our Giardia cases fail to show Giardia a couple of years after giving the drug. It has been a couple of years since we started this drug.

It is interesting that Hemeter was the first to talk about Giardia in America, in this Association in 1925, as mentioned Dr Lyon and I reported our first twenty cases. Nineteen of the twenty we believe had a disease of the duodenal biliary zone, and I noticed Dr Welch had quite a few associated with the pyloric dysfunction duodenitis, and duodenal ulcer.

Dr Hartman mentioned he is not sure what the parasite does. We reviewed the literature extensively, and we found that the Giardia will adhere by the millions to the duodenal surface, and also found one investigator, who discovered that it even penetrated the duodenal mucosa into the lower coats so if this occurs, one can assume that duodenitis or jejunitis can at least be set up and in all these conditions dyskinesia and sphincter spasm can occur.

At Temple, one case was sent to the clinic apparently with carcinoma of the liver. We discovered in our usual studies Giardiasis, and we treated the case inasmuch as we thought it inoperable. To our surprise, the liver went down to normal later on and the patient is still living. All we did was to attack his giardia. That was a rare case but it did actually happen.

I want to stress at this time that I believe Dr Welch has brought up a very important paper. I notice Drs Hartman and Kyser in their series of 100 cases had only eleven cases in which there were no symptoms attributable to the parasite. This is an important statement coming from a clinic so well known as the Mayo Clinic.

DR WILLIAM C BOECK (Los Angeles) I have probably seen these cases more than anyone here. I was interested in them first as a protozoologist and later after I became a medical man, to see whether my opinion would change regarding the symptomatology of these cases. I think the symptoms we had listed here might well be the same ones for a number of functional disturbances, and the finding of Giardia in the stool and in duodenal aspirates is purely incidental, but immediately because you find it, you start to attach significance to it.

If all these symptoms are true for Giardia infections then I think the field of pediatrics has a marvelous chance to contribute to the field of gastro-enterology because the incidence of giardiasis in children is anywhere from twice to four or more times what it is in adults. Therefore, nature, somehow or other, must get rid of those infections by the time we grow up. Certainly you do not find in children, at least most pediatricians do not—most of the symptoms referred to and pediatricians with some exceptions, are not talking about invasion of the biliary tract or duodenitis in their patients. They mostly focus on the point of diarrhea, and say that diarrhea is worse if the infestation is severe, but that is entirely dependent upon how many parasites you visualize in the stool, and that is no measure of the infection, any more than the number of *Endameba histolytica* in the stool is a measure of how severe the amebic colitis may be.

I think this question of the pathogenicity of Giardia should be considered a little more gravely, perhaps, and with more reserved consideration. I believe that in Dr Hartman's case in which he found the organisms in the gall bladder—he couldn't be sure that Giardia produced a cholecystitis, and certainly the earlier reports of this parasite producing cholecystitis are not dependable.

I know the case referred to by Dr Swalm in which Giardia is supposed to have penetrated the mucosa, and I submit that the microscopic sections were not good preparations and the invasion can be explained by artefacts, just as *Trichomonas* said to be invading the epithelium in the bowel.

I think that is all

DR MANFRED KRAEMER (Newark, N J) In 1933 I wrote a paper on Giardiasis, reporting thirty-three cases and concluded that Giardia lamblia was a commensal parasite for man. Many of my friends disagreed with me, but I thought I was very right about the subject.

A year or two later I saw Dr Swalm and he said 'Kraemer, if you ever get another case of giardiasis, I think I have something that is good. I wish you would try it.' This was Atabrine.

At that time a patient came in with a very severe diarrhea and evidence of duodenitis, and also proctocolitis, as noted by Dr Welch in one of his cases. The stools were swarming with Giardia. He responded to no treatment until I tried Atabrine, for the first time in months the diarrhea ceased. The patient was kept under observation and the diarrhea never recurred.

Then we had another patient harboring Giardia in whom we had considered chronic cholecystitis as the cause of illness. He had suffered with the same diagnosis for some ten or twelve years. He had had our previous treatment for giardiasis: arsphenamine lavage, gentian violet, repeated Lyon drainages, etc.

He was then given a course of Atabrine. Biliary drainage two weeks later showed no Giardia in the duodenal content, for the first time in many years. I did not see the patient again until last week, when he told me that he wondered if it wouldn't be worth while just to see if 'they' had come back, though he had been feeling well in the interim. None were found.

On the basis of these two cases and others which I have seen since I am forced to change my opinion and say that the symptoms associated with Giardia are not on a functional nervous basis, and that they are real.

Dr Welch has made a further worthwhile contribution to the subject

Thank you

DR WILLIAM C BOECK (Los Angeles) May I have one more word? I want to report a case which has had four courses of atabrine and so far he still has his *Giardia*

DR LESTER MORRISON (Philadelphia) Doctor Welch has added to our knowledge relative to the pathogenicity and anatomic changes that can be attributed to infection with *Giardia lamblia*. The trophozoite lives in the duodenum and to the present time we have no knowledge as to how it can produce symptoms of disease in the upper part of the digestive tract. Perhaps as Doctor Welch reports, spasticity of the duodenum in the presence of giardiasis is the immediate cause of symptoms but we still have to know how the organism can cause anatomic deformity. In the Mayo Clinic we have treated approximately seventy-five patients infected with giardiasis with atabrine since this effective medicine was announced in 1937 as effective against this particular parasitic disease. In our small series of patients we have had only one failure in the course of treatment. I would like to ask Doctor Welch what he means by a course of treatment. In the clinic fifteen tablets of 0.1 gm constitute a course, the dose is one tablet three times a day. It could be assumed that such a parasite as *Giardia* could produce eosinophilia as reported by Doctor Welch, but in our series of cases we have not checked the blood for this particular finding.

DR PAUL B WELCH (Miami) (closing the discussion) I little expected that this presentation would

initiate such a diversity of opinion as expressed by its discussors

Dr Boeck, about one year from now, upon completing our studies on a large series of cases of giardiasis in children, I will be able to answer you more specifically and authoritatively. The cases reported today were mostly adults. No claim is made that the symptoms tabulated are specific for giardiasis. I do think that they are more or less characteristic of irritation in the pyloric, prepyloric area and duodenum.

Our course of treatment, Dr Hartman, is the same as yours. So far in one instance we had to repeat the course of atabrine three times without any harmful effect, though we allowed a period of approximately two weeks to intervene between the series of treatments. In this case it was a doctor's son and he had his appendix taken out, without relief, because of the giardial symptoms, and a diagnosis was previously made of pyloric hypertrophy.

I think this patient was resistant to treatment possibly because of the high degree of pyloric stenosis associated with the pyloric hypertrophy. Incidentally, this pyloric obstruction disappeared after the third course of atabrine and the re-examination six months later showed an approximately normal pyloric function.

I haven't had a large series of cases, that is, large enough to venture an opinion as to the infallibility of atabrine. Certainly it is much better than the terrible measures used formerly, such as De Rivas' heat treatment, which sometimes put the patient in shock, trying to get rid of the *Giardia*, and I am extremely thankful we have atabrine as a specific agent for this infection.

I want to thank you all again for your very, very interesting and enlightening discussion.

The Chemotherapy of Chronic Ulcerative Colitis

By

MOORE A MILLS, M D, Ph D

and

THOMAS T MACKIE, M D

NEW YORK NEW YORK

CHRONIC ulcerative colitis presents one of the more difficult therapeutic problems with which the Gastro-Enterologist and Internist is confronted. Our present philosophy of the disease and the basis of our therapeutic approach, envisions ulcerative colitis as a polyvalent disease, the primary etiology of which is imperfectly understood, and the fundamental pathogenesis of which is nonspecific infection of the colon with any of a variety of organisms of mixed pathogenicity. As the disease process progresses, and secondary to it, a number of factors may develop which play a major role in the activity and symptomatology of the disease process. Foremost among these secondary factors are mixed deficiency states, marked disturbances of intestinal physiology, especially of motor function, various psychogenic disorders, focal infection of the nose and throat, and, the development of allergic states, including bacterial allergy, and allergy to foods.

The successful medical management of any case of ulcerative colitis must be based upon an exhaustive study of the case to determine the presence and

magnitude of the above mentioned factors, and entails in addition, the correction of and protection against deficiency disease, the correction of disturbances of physiology in the gastro-intestinal tract, the control of anemia, and the identification and management of the allergic states. The control of the factor of infection in the colon has hitherto been the most difficult of accomplishment. In the past, such efforts have been limited to the local application of medicaments by clysmas, a procedure which aggravated the already hyperirritable colon more often than it benefited the condition, and by the use of vaccines and sera. The latter have been of benefit in a certain number of cases but on the whole, results obtained with these instruments have been only partial, or at best, transitory. The advent of the sulfonamide drugs has therefore opened new possibilities of attacking the fundamental factor of local infection in the colon, at least in cases in which the dominant infectious agent proves susceptible to their action.

The present communication deals with the use of three of the sulfonamide derivatives—sulfathiazol, sulfaguanidine, and sulfadiazine, in one hundred and nine unselected cases of ulcerative colitis from the

colitis clinic of the Roosevelt Hospital. All types of cases, from acute and fulminating cases to chronic cases with extensive pathologic changes in the colon have been included. The diagnosis in each case was made on the basis of the history, proctoscopic examination, and X-ray evidence. All cases on therapy were examined at intervals of one or two weeks at which time they were proctoscoped, cultures taken through the proctoscope, and in addition, blood levels of the drug, blood counts and urine studies performed.

TABLE I
Sulfathiazol

Type of Cases	Markedly Improved	Definitely Improved	Not Improved	Drug Intolerance	Total
Acute	8	1	2	1	12
Active	13	18	5	1	37
Chronic	1	3	1	1	6
Recurrences	1	1	0	2	4
Convalescent	0	0	0	0	0
	23	23	8	5	59

Before chemotherapy was employed all (except the more acute cases) were studied for the presence of the secondary factors which have been mentioned. These were corrected insofar as it was possible. Each case was maintained upon a high protein low carbohydrate diet, with supplements of iron, vitamins and liver extract in deficient cases. Sedatives and antispasmodics were frequently indicated. Sodium sulphate was employed for the correction of caecal stasis, an aberration of the motor function of the colon in approximately half the cases during the treatment period.

The results of chemotherapy are included in separate tables for each drug. Thirty-six of the cases were treated with only one drug. The remainder received more than one of the drugs at intervals or in sequence during the period of observation. In the latter case the results obtained with the separate drugs are included in the tabulation of results under the respective drugs. Thus, there are a total of two hundred twenty-one observations of therapy in the total of one hundred nine cases.

To facilitate analysis in tabulation of results, the cases are divided into five groups on the basis of the activity of the disease process at the time therapy was instituted, namely (1) acute cases, which include all cases with high, often septic, temperatures, severe diarrhea with excessive bleeding, severe abdominal cramping and a proctoscopic picture of acute inflammation with edema, ulceration and free bleeding, (2) active cases, with bloody diarrhea, cramps, and on proctoscopy, active inflammation and ulceration, (3) chronic cases which are distinguished from active cases by the chronic nature of the picture on proctoscopy and the duration of the symptoms without significant variation, (4) early recurrences cases previously quiescent, presenting evidence of recurring activity of the infectious process, and (5) convalescent cases, which include cases treated with one of the drugs during an acute or active phase of the disease

with improvement, who have been changed to the tabulated drug for prolonged therapy.

The results of therapy are included in three categories: markedly improved in which cases the active disease subsided and the disease became quiescent while on therapy, definitely improved, cases which responded favorably to drug therapy but in which complete healing was not observed on proctoscopic examination or in which a recurrence of activity occurred within three months after discontinuing therapy, not improved, and, drug intolerance, which latter includes cases in which the drug aggravated the disease process in the colon. This category is not to be confused with toxic reactions due to any of the drugs.

Sulfathiazol was employed in fifty-nine instances, the results of which are included in Table I. The drug proved most effective in acute cases, less so in cases designated as active. The explanation for this probably resides in the relatively high toxicity of sulfathiazol as compared with the other two drugs studied, and in our unwillingness to use the drug in ambulatory cases for prolonged periods of time. There were fourteen instances in which toxic reactions to sulfathiazol developed (24%), and five instances of gross hematuria. The dosages employed included an initial dose of six grams divided in six equal doses which was reduced to four grams in twenty-four hours after several days. The average total dose administered was forty grams per case.

Sulfadiazine was given to seventy-one cases of ulcerative colitis (Table II). Of this group, 35 or 50% were considered to be markedly improved and twenty one or 29% were definitely improved, a total of fifty six or 79% in which sulfadiazine favorably influenced the course of the disease. Fifteen cases were not improved or were intolerant of the drug, and four cases developed toxic manifestations after a short course of therapy. The dosages employed were not calculated on the basis of body weight, a standard dose of three grams per day in divided doses being employed in adults and 1.5 gram doses in children. Several cases

TABLE II
Sulfadiazine

Type of Cases	Markedly Improved	Definitely Improved	Not Improved	Drug Intolerance	Total
Acute	4	2	0	1	7
Active	15	6	5	3	32
Chronic	0	5	3	0	8
Recurrences		1	1	2	4
Convalescent	5	4	0	0	9
	35	21	9	6	71

in this series were maintained on a dose of three grams daily for periods in excess of three months without deleterious effects being encountered. Total doses of this series averaged between 100 and 150 grams. Sulfadiazine was especially valuable in cases in which upper respiratory infection was an important factor. It is considered the drug of choice in all cases of ulcerative colitis.

Sulfaguanidine was administered to ninety-one individuals (Table III). Seventy-five of these cases (82%)

were definitely improved on therapy with this drug. This satisfying figure was achieved only after it was found that the duration of constant therapy was of greater importance than dosage, type of pathology, or bacterial flora. Sulfaguanidine was of no value in fulminating cases, or in cases with severe diarrhea, although the drug was used with gratifying effect in the same individuals after the acute process had been tempered by treatment with one of the other drugs. The dosages employed, as with the other drugs, were not computed on a basis of body weight. It was soon found that small doses were as effective as the larger amounts, and the dosage ultimately used was six

TABLE III
Sulfaguanidine

Type of Cases	Markedly Improved	Definitely Improved	Not Improved	Drug In tolerance	Total
Acute	0	0	2	0	2
Active	18	17	4	3	42
Chronic	4	14	2	1	21
Recurrences	8	3	3	1	15
Convalescent	11	0	0	0	11
	41	34	11	5	91

grams per day in three doses at eight hour intervals. This amount was reduced to three grams when feasible, in each case. The duration of treatment averaged 8 weeks, and total doses given averaged in excess of 300 grams.

The present status of the 109 individuals included in this series is contained in Table IV, with the final results of therapy analyzed in terms of the type and extent of the pathology found in the colon. Fifteen of the cases have been in a sustained remission of the disease for periods of six months to two years. In 35 cases the disease process is quiescent both on proctoscopic examination and symptomatically, but these individuals are as yet on active therapy. Twenty-five cases are on active therapy with continuing improvement in their disease. Seventeen of the cases (15.5%)

are unimproved. Seven cases have had ileostomies performed during the three year observation period. There were four deaths in the series (3.6%) and in six instances the present status is unknown. As might be expected, the better results are found in cases without severe and irreversible pathologic changes in the colon. However, organic changes in the colon short of obstructing stenosis, cannot be considered primarily surgical until adequate chemotherapy has been employed. Twenty-four cases in the series were proved to have an idiosyncrasy to some article of food, and in seventeen others food allergy was suspected on the basis of clinical observation. There was no correlation between food allergy and the response to chemotherapy.

Routine bacteriologic cultures revealed a wide variety of organisms of varying degrees of pathogenicity. We were unable to correlate the bacterial flora with the response to drug therapy. Further studies are in progress which may yield more definite information on this subject.

Every possible precaution was taken to prevent confusion of spontaneous remissions of the disease with responses to drug therapy. In all cases in which improvement occurred with protracted chemotherapy, the drug was omitted at intervals in the course, and evidence of recurrence of activity without therapy noted. No placebos were employed in this study.

SUMMARY

Sulfathiazol, sulfadiazine, and sulfaguanidine were employed in 109 cases of ulcerative colitis. Definite or marked improvement was obtained in 78% of these cases with the drugs. Sulfadiazine has proved to be the drug of choice for all variety of cases. Sulfaguanidine is of definite benefit in the majority of cases without excessive diarrhea, and should be employed for prolonged periods of time. None of the drugs should be in any way considered as specific in this disease. No cases can be considered to be cured by chemotherapy.

DISCUSSION

DR LEON BLOCH (Chicago) Madam President and Members of the Association: From time to time as new forms of treatment for ulcerative colitis appeared it looked as though advances were being made. Neoprontosil,

TABLE IV

Present Status	Total Cases	Grade of Pathologic Change			Food Allergy		
		3	2	1	Proved	Suspected	No Allergy
Sustained remission	15	1	1	13	3	4	8
Quiescent on therapy	35	7	6	22	6	4	25
Improving on therapy	25	4	11	10	5	4	16
Not improved by therapy	17	6	7	4	5	5	7
Surgical cases	7	4	2	1	2	0	5
Dead	4	0	1	3	1	0	3
Unknown	6	1	1	4	2	0	4
	100	23	29	57	24	17	68

Code: Pathologic change
 3—Extensive deformity with obstructing stenosis
 2—Shortening polyps extensive fibrosis without stenosis or obstruction
 1—Ulceration spasm moderate fibrosis
 Allergy to foods
 Proved—By addition and withdrawal of suspected foods
 Suspected—Improved on test diets (clinical) but not definitely proved

sulfathiazole, sulfapyridine, sulfanilylguanidine, and sulfasuccinyl at first seemed to have some value, but none were really efficacious.

Because of the interest aroused in topical application of the sulfone drugs, I tried to use one of them in the form of retention enemas. About a month ago I saw a child of nine with ulcerative colitis in the Michael Reese Hospital, who had been sick for several months and whose temperature had ranged from 101 to 105 at various times. None of the sulfone drugs administered previously had any effect. Retention enemas of an 0.8% aqueous solution of sulfanilamide were followed by a drop in the temperature in thirty-six hours. A few days later an elevation of the temperature recurred and the drug was stopped. The same type of treatment was used in a young woman with chronic ulcerative colitis. An ileostomy was necessary because the ileum had become matted into a tumor-like formation with the development of symptoms of obstruction. Although the general symptoms subsided after the operation and the patient had gained considerable weight the proctoscopic appearance of the sigmoid changed very little until three weeks after the institution of treatment with daily retention enemas of 0.8% aqueous solution of sulfanilamide combined with 45 grains of sulphathiazole daily. Large doses of this drug previously had no effect. At this time the sigmoid assumed a light pink color where previously definite ulcerations and marked hyperemia were seen. Two weeks later the mucous membrane assumed an almost normal color. This form of treatment is not recommended as a cure-all but is offered simply as a suggestion where other types of treatment have been tried unsuccessfully. Only recently it has been shown that the rectum and colon can absorb enough of the sulfone drugs to cause a very definite rise in the blood level.

DR ASHER WINKELSTEIN (New York) Dr Jordan and Friends: I found Dr Mills' paper very interesting. However, the high percentage of good results which he reported here was quite startling and contrary to our experience. Our viewpoints may be presented as follows:

Studies of indeterminate ulcerative colitis over a period of many years have revealed the following: A small percentage, perhaps 3 to 5, are unrecognized cases of amebic colitis, a larger percentage, perhaps 15, are chronic bacillary dysentery, what the nature of the rest is, seems as yet unknown.

Repeated cultures from ulcerated areas and biopsied tissue have yielded only hemolytic and non-hemolytic *B. Coli* and enterococci in our laboratory.

Since the introduction of the sulfonamide drugs, we have used in the treatment of ulcerative colitis, sulfanilamide, neo-prontosil, sulfapyridine, sulfadiazine, sulfaguanidine, and the latest intestinal antiseptic, sulfasuxidine.

Our results have been almost uniformly disappointing. A rare good result occurred, which was to be expected in view of the fact that ulcerative colitis is characterized by a strong tendency to spontaneous remissions. Since these drugs, particularly the intestinal antiseptic drugs, sulfaguanidine and sulfasuxidine, act powerfully against the colon bacillus we must surmise that this disease is possibly caused by some other organism. Perhaps the dosage and mode of administration of these drugs should be altered. We have tried combinations of sulfadiazine or sulfathiazole, plus sulfaguanidine or sulfasuxidine given simultaneously, with the idea of raising the blood level of these drugs to attack the organisms in the tissues (if they are there) and at the same time attacking the organisms in the lumen of the bowel. Thus far this method, tried in a few cases, has also been a failure. Despite the advent of the sulfonamides, we still feel that the best treatment of severe cases of indeterminate ulcerative colitis consists in repeated transfusions, concentrated antitoxic *B. Coli* serum

intramuscularly (Winkelstein and Schwartzman), and various surgical procedures. Despite this conclusion, we are not opposed to the administration of the sulfonamide drugs in this disease.

DR JOSEPH B. KIRSNER (Chicago) At the University of Chicago we have been conducting a more or less systematic study of the effect of various sulfonamides on the clinical course of ulcerative colitis and also on the bacteriology of the feces. We have used sulfanilamide both by mouth and as retention enemas, neo-prontosil or azosulfamide, sulfathiazole, sulfanilylguanidine, and succinyl sulfathiazole.

We have noted that all these drugs exert a somewhat similar action on the bacterial flora of the feces. Sulfanilylguanidine, for example, rapidly decreases the total aerobic bacterial count, and several days after the onset of such therapy, the count may drop from a level of one thousand million colonies per gram of feces to as low as one million colonies per gram of feces. The organisms which remain consist of the green streptococcus, staphylococci, gram-positive, spore-bearing bacilli, yeasts, and molds.

Cessation of sulfanilylguanidine therapy is followed by an equally prompt return in the bacterial count to previous levels. Sulfanilamide apparently exerts a similar action, as do sulfadiazine and sulfathiazole.

It was originally held that sulfanilylguanidine was poorly absorbed from the intestinal tract. We have observed blood levels as high as 10 or 11 milligrams per cent when the drug is administered in doses of 10 or 15 grams daily, and I know of one case in which the blood level of sulfanilylguanidine rose to approximately 16 milligrams per cent.

In our experience sulfanilylguanidine has been less toxic than other previously used sulfonamides. In a series of approximately twenty patients, we did observe a toxic dermatitis in four cases, and, in one case, a toxic granulopenia. These manifestations subsided promptly when the drug was discontinued.

Our series with succinyl sulfathiazole is too small to permit any definite conclusions regarding toxicity, but thus far we have not observed any toxic reactions and the blood count and urine remain normal.

In accord with Dr Winkelstein's experience, our therapeutic results have not been striking. We have occasionally observed a patient who seemed to improve during chemotherapy. The improvement, however, was temporary, and when the drug was discontinued we thought the clinical symptoms increased. The proctoscopic appearance of the rectal and sigmoidal mucosa similarly showed recurrent inflammation. Furthermore, those patients who did seem to improve consisted of the mild or moderately severe types of ulcerative colitis, in whom we have observed similar and even more striking improvement without any specific therapy, that is, after the use of bed rest, sedatives, and a bland diet.

I should like to end this discussion on a note of conservatism. I do not need to tell you about the natural history of chronic non-specific ulcerative colitis, and I am sure that all of you have seen startling improvements in these patients without any specific therapy. I think the continued use of sulfonamide drugs is highly justifiable and may lead to the discovery of a more effective preparation, but a careful and controlled evaluation of therapeutic results is necessary.

Thank you.

DR J. ARNOLD BARGEN (Rochester, Minn.) The Program Committee put this paper on because it seemed timely for many of us to air opinions on the subject of chemotherapy and ulcerative colitis, and they put it last on the program so that whatever time was left could be employed in its discussion.

I thought it was important to again call attention to a fact on which Dr Winkelstein has touched, namely, that there are many different types of ulcerative colitis. A variety of opinions concerning the etiology of ulcerative colitis have existed. As experience grew, the one apparent fact was that ulcerative colitis was not "all of a type," and so we at the clinic have learned to think of "chronic ulcerative colitis" not as a disease entity but rather a syndrome in which various entities are developed. I want to emphasize here that we are not thinking of "chronic ulcerative colitis" in the idiopathic sense, but rather in the sense of many disease entities with established etiology. Thus we have streptococcal ulcerative colitis, tuberculous ulcerative colitis, amoebic ulcerative colitis, lymphopathia venereum ulcerative colitis, that form which represents a late form of bacillary dysentery, allergic colitis, a deficiency syndrome, and then we still have a sizeable group of patients, although this group has become smaller with increasing knowledge, the nature of whose colitis we do not understand. That latter includes some of the regional forms of ulcerative colitis, in which the lesions are so different than the streptococcal type and all other types that we can readily classify them by themselves. I am sure that as knowledge increased it will be found that among these cases a number of other entities exist.

To use chemotherapy properly then, in our experience, it is important to treat on the basis of etiology. Leaving out now amoebic ulcerative colitis and tuberculous ulcerative colitis, the other forms respond in accordance with their cause providing other supplementary measures of therapy are employed.

I don't know why Dr Mills didn't use neoprontosil, but it can be said that the streptococcal type, to date, in spite of failures here and there, responds best to neoprontosil. We have used other drugs—all those that have been mentioned—and all of them seem to help some cases but we find that the response of individual cases of a group varies with individual drugs of the series, the "idiopathic," or the group of which we still don't understand the cause, has responded best in our hands to sulfathiazole and sulfanilylguanidine, and more recently to the succinyl sulfathiazole.

All these drugs have their advantages and the manner of giving them is of utmost importance. The concentration of the drug in the blood should always be followed, no matter how much of the drug comes in contact with the intestinal mucosa. We have been able to sterilize the intestine as far as gram negative organisms are concerned, and sometimes as far as streptococci are concerned as well, but this affect does not seem to run parallel with the results of treatment. The amount of a drug in the blood rather determines what results one can expect, so with neoprontosil 3.5 mg per cent, sulfanilylguanidine 3.5, with sulfathiazole 10 to 12 and with sulfasuccidine or succinyl sulfathiazole 1½ to 2 mg per cent.

As to the amount of a drug to be given, or the length of time to give it, we have adopted a policy of never giving it longer than two weeks. In that two weeks we give large doses, then rest the patient a week, and then give it again.

I have found patients, individual cases, to obtain toxic effects from all of these drugs, sometimes when least expected. I have seen a young girl go into shock and break out in an acute rash on two grams of sulfanilylguanidine, whereas the average individual takes 10 to 15 grams in twenty-four hours.

I would like to call attention to the fact that the last drug mentioned, i.e., succinyl sulfathiazole, may be given to cases who could not tolerate various of the others. Even when patients had severe toxic reactions from neoprontosil or sulfaguanidine, they could take succinyl sulfathiazole.

In summary, when you use these drugs think first of the etiology, then see which drug is the reasonable one to use, and then give enough of the drug to get a certain definite concentration in the blood.

DR MOORE A MILLS (New York) I am sorry that the time for the presentation of as much evidence as we have collected necessitated paring down to practically sentences, material which could well have been conveyed in paragraphs.

We feel, first, that in cases of ulcerative colitis observed over a long period of time, unless all of the factors bearing on the disease, as mentioned in the early part of the paper, are taken into account, final results are necessarily going to differ from these which we have reported.

Dr Andriesen recently has written on food allergy in ulcerative colitis and reported a large number of cases in which one or more foods constituted the immediate factor in the diarrhea and in the activity of the colitis. In our series 35% were felt to give clinical evidence of food idiosyncrasy, and if, in these cases the treatment did not include the elimination of that factor, our ultimate results would have been distinctly different.

In addition to that, a point which Dr Winkelstein has brought up, we have carefully studied all of these cases for types of colitis, and the majority of them have been given emetine and carbarsone, despite repeatedly negative stool studies, to rule out amoebae. We feel that hemolytic *B. coli* is perhaps one of the more common, if not the most common, organisms to which these patients react. We have several case histories which bear this out.

I have purposely had to omit the use of other drugs in this paper, although we have used neoprontosil, succinyl sulfathiazole, and sulfanilamide. Several of the cases with hemolytic *B. coli* have responded very well to these drugs on long-continued administration. The duration of treatment is exceedingly important. One of our cases was absolutely quiescent on two grams of sulfanilylguanidine given three times daily at eight-hour intervals. We reduced it to one gram and a moderate recurrence of activity resulted after four or five days. We were able to vary his symptoms at two-week intervals by varying the dosage of sulfanilylguanidine.

I couldn't, as I say, mention the use of vaccines or sera because of the time limitation and the confusion which would naturally result from multiplying the therapeutic agents.

With regard to Dr Bargen and the question of neoprontosil, I think careful analysis of our data would indicate that these drugs do not cure ulcerative colitis, but merely that a definitely large percentage can be improved by their use. The distribution of our cases, as "arrested," "improved" and "no change," is similar in all respects to Dr Bargen's report on sulfanilylguanidine, which appeared a short time ago. We couldn't include our use of neoprontosil or succinyl sulfathiazole in ulcerative colitis. With these drugs we have obtained results similar to those included in this report.

The Significance of Hemorrhagic or Pigment Spots as Observed by Gastroscopy*

By

JULIAN M. RUFFIN, M.D.†

and

IVAN W. BROWN, JR., M.D.‡

DURHAM, NORTH CAROLINA

WITH the exception of ulcer or carcinoma, one of the most striking changes observed in the gastroscopic examination of the stomach is the so-called hemorrhagic or pigment spot. These spots (Fig 1) are sharply circumscribed areas which stand out clearly against the orange-red background of the gastric mucosa. They vary from one to five millimeters in diameter and usually occur on the crests of the folds, apparently just beneath the surface of the mucosa. They range in color from a bright red to brown or black and may be surrounded by a red halo. Some have been described as being "star-shaped" (1) but in our experience most of the spots have appeared round or oval.

There has been considerable discussion as to the significance of these spots, certain observers (2, 3, 4) believing that they are in some way related to ulcer formation, while others (5) state they have no significance whatsoever. They have been referred to as "chronic localized gastric purpura," constituting "not

suggested that the spots were probably an incidental finding and of no significance.

In the preparation of the patient for gastroscopy it is customary to empty the stomach by introducing a tube and removing the contents either by gravity or by aspiration. In this Clinic aspiration is generally employed. Purely by accident, it was noted that these spots were usually seen if the patient's stomach was aspirated prior to the gastroscopic examination and conversely, rarely observed if aspiration was omitted. With this observation in mind the following study was undertaken.

EXPERIMENTAL STUDIES IN MAN

One hundred and eighteen patients who had negative roentgenograms of the stomach were aspirated in the usual manner. A duodenal tube with an olive tip was used and the same suction employed as in the case

TABLE I

	No. Cases	Spots Observed	Per Cent
Aspirated	118	76	65
Not aspirated	122	6	5

only a new but also an important disease" of the stomach (6).

In a report (7) from this Clinic some years ago in which the gastroscopic findings of 240 apparently normal patients were analyzed, it was found that hemorrhagic or pigment spots were observed in twenty-five per cent of the cases. It was shown that these spots had no significant relationship to the age of the patient, to diet, to the use of alcohol or tobacco, to the presence of an anemia, or to the degree of acidity. Nor was there any definite clinical picture associated with them.

CLINICAL OBSERVATIONS

It has been pointed out that these spots may come and go without apparent effect upon the patient. In our experience it was frequently noted that spots which had been present at a previous examination had entirely disappeared a few days or weeks later. This

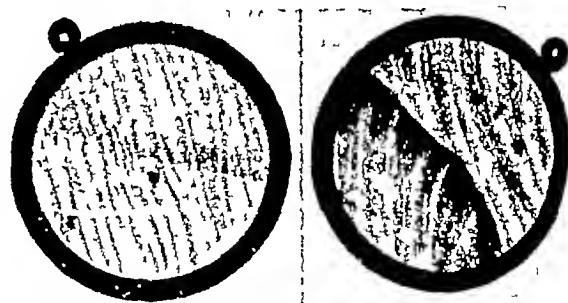


Fig. 1. Drawings of typical hemorrhagic or pigment spots as seen through the gastroscope.*

of an ordinary gastric analysis. These patients were then gastroscopied and pigment spots were observed in seventy-six or sixty-five per cent of them. In a similar group of one hundred and twenty-two patients who were not aspirated, spots were seen in only six, or five per cent (Table I). Five other patients were gastroscopied and the mucosa was found to be entirely normal; there being no evidence of hemorrhage or pigment spots. Then their stomachs were aspirated and fifteen minutes later were gastroscopied again. In two nothing abnormal was noted, but in the other three patients typical spots were observed.

There was no constant relationship between the degree of acidity and the color of the spot. However, in the absence of acid the color was usually red or reddish brown. With a high degree of acidity the spots

*From the Departments of Medicine and Pathology, Duke University School of Medicine, Durham, North Carolina.

†Associate Professor of Medicine, Duke University School of Medicine.

‡Senior Assistant in Pathology, Duke University School of Medicine.

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*Colored drawings illustrating pigment spots are shown in article, "The Effect of Inflation of the Stomach Upon the Gastroscopic Picture," published in the American Journal of Digestive Diseases, October, 1940.

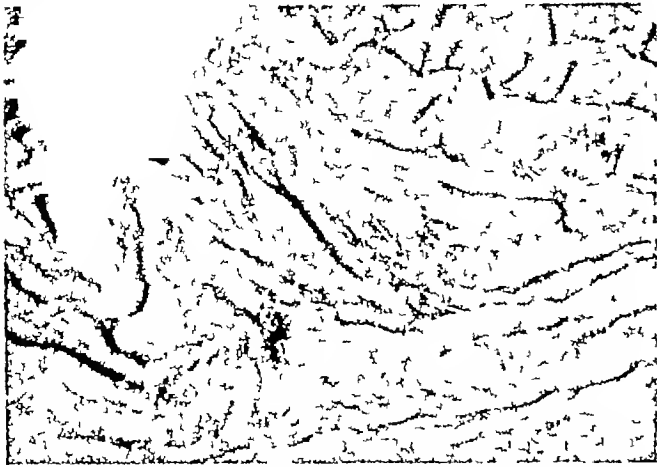


Fig 2 Photograph of stomach in Case 2. Pigment spots shown by arrows

were black as a rule, though occasionally red spots were seen when free HCl was present in normal amounts. The following cases are reported, as they afforded an opportunity to study these spots in greater detail, both clinically and pathologically.

CASE REPORTS

Case 1 Through the courtesy of Dr. Stewart Wolf and the staff of the New York Hospital, a patient having a gastrostomy was studied. The patient, T. L., age 56, had had a gastrostomy forty-six years ago because of a stricture of the esophagus. The exposed gastric mucosa was red, swollen and slightly edematous. However, the mucosa within the stoma as seen through the gastroscope, which was introduced through the gastrostomy opening, appeared fairly normal. Then the duodenal tube was introduced and the tip located through the stoma by means of the gastroscope. Aspiration produced hemorrhagic areas which after ten minutes became brown and later developed a red halo. Twenty-four hours later these spots had disap-

peared, leaving an apparently normal mucosa. The spots could be produced at will, and their size varied directly with the amount of suction applied. On one occasion very black spots followed aspiration. The smaller ones disappeared after twenty-four hours, but the larger ones persisted for forty-eight hours or longer, fading gradually and finally disappearing entirely, leaving no trace. These spots were identical in appearance with those described earlier in this discussion. The free HCl in the gastric secretion was 75° at the time of study.

Case 2 M. J., a 54-year-old white female was admitted to Duke Hospital February 3, 1942, with a history of gall bladder colic of four days duration. Except for similar attacks in the past she had had no digestive disturbances. The routine physical examination showed nothing of significance. By X-ray she was found to have a poorly functioning gall bladder. Gastric analysis showed no free HCl after histamine.

On February 7, 1942, her gall bladder and appendix were removed. The gall bladder contained numerous stones. On February 13, 1942, she began having a low grade fever, for which no cause could be found. On February 15, 1942, the stomach was aspirated because of nausea and epigastric distention. Two hours and forty minutes later the patient suddenly expired from a pulmonary embolus, originating from a thrombus in the left iliac vein. Autopsy was performed immediately, the stomach removed and immersed in formalin. Numerous hemorrhagic spots similar to those already described were observed (Fig 2).

Grossly, the spots appeared as fresh hemorrhages beneath the surface of the mucosa, sharply circumscribed and slightly raised. Over some of them there was seen a dirty, grayish membrane. They occurred chiefly on the crests of folds and, on section, they were found to be entirely limited to the mucosa. Elsewhere, the gastric mucosa appeared normal. Microscopic sections through these areas showed focal hemorrhages, most marked in the superficial layers of the mucosa. Some spots showed early necrosis and sloughing of the superficial mucosal layers with a moderate leukocytic infiltration of both mucosa and submucosa (Fig 3).

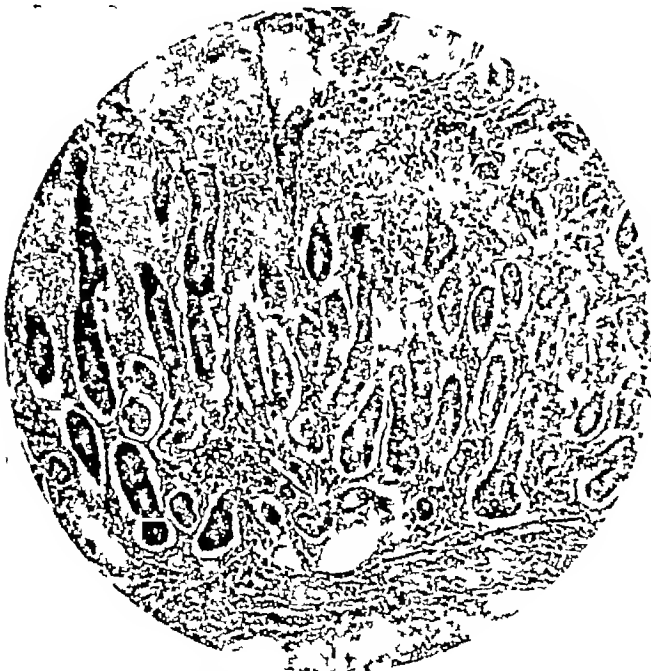


Fig 3 Photomicrograph of stomach, Case 2, through pigment spot showing hemorrhage into interstitial tissue with early disorganization of superficial epithelium and mild leukocytic infiltration



Fig 3a Photomicrograph of stomach, Case 2, through area not showing pigment spots

EXPERIMENTAL STUDIES IN ANIMALS

Five dogs were studied. Using sodium amytal intravenously as an anesthetic, the gastroscope was passed and in each instance nothing abnormal was observed. Then the duodenal tube with an olive tip was introduced simultaneously with the gastroscope and the position of the tip in the stomach noted. Without removing the gastroscope, suction was applied and the mucosa studied immediately. In every case hemorrhagic areas were produced which later became black. These were two to five millimeters in diameter and were slightly raised. It was noted, as in the case of the patient with a gastrostomy (Case 1), that the size of the hemorrhages varied directly with the amount of suction applied.

While the animal was still alive, the stomach was removed and immediately immersed in Helly's fluid. Grossly, one observed in each stomach hemorrhagic areas which varied from small hemorrhages appearing beneath the surface of the mucosa, on the crests of folds to much larger ones, suggesting "blood blisters." Microscopic sections (Fig. 4) through some of these areas showed fresh localized hemorrhages within the mucosa with the superficial mucosal layers intact. In others, the hemorrhage penetrated to the submucosa with early necrosis and sloughing of the epithelium. The mucosal vessels were congested and ruptured and superficially there was laking and hemolysis of the erythrocytes. In many affected areas, the mucosa and adjacent submucosa were edematous.

DISCUSSION

The interpretation of changes in the gastric mucosa as seen by gastroscopy has led to much discussion and considerable controversy. Obviously, gross lesions such as ulcer or carcinoma can cause symptoms which are readily described by the patient, and certainly no one would question the fact that an acute gastritis may result in a fairly typical clinical picture. But there is

still some doubt in the minds of many clinicians as to the relationship between the patient's symptoms and minor changes in the gastric mucosa or deviation from what is thought to be normal in small localized areas of the stomach. In this connection it should be pointed out that a patient may have a gastric ulcer or carcinoma and still have at the time no symptoms whatever. The existence of chronic gastritis can hardly be questioned, but that it is the cause of the patient's symptoms is quite another matter.

The danger of assuming that minor localized changes in the gastric mucosa are the cause of subjective sensations is well illustrated by this study. There was no correlation whatever between the patient's symptoms and the presence of the hemorrhagic spots. Spots were seen also in normal students who had no symptoms referable to the stomach, and it should be emphasized that no symptoms developed in those patients in whom the spots were produced experimentally. This was clearly the case in the patient with the gastrostomy (Case 1) in whom spots were produced at will, and gave rise to no symptoms whatever. Our observations point conclusively to the fact that these spots may develop as result of trauma to the gastric mucosa and do not produce subjective sensations in the patient. In this connection it should be pointed out that a positive benzidine in the usual gastric analysis is of common occurrence and for the most part has no significance.

It is realized, of course, that spots may occur in the absence of aspiration of the stomach, since many gastroscopists (2, 5, 8, 9, 10), who empty the stomach contents by gravity have reported their occurrence. The cause of the spots in the absence of known trauma is a matter of speculation. However, such factors as coarse foods, hyperperistalsis, and vomiting must be considered as possible explanations. The passage of the gastroscope itself may, in some instances, trauma

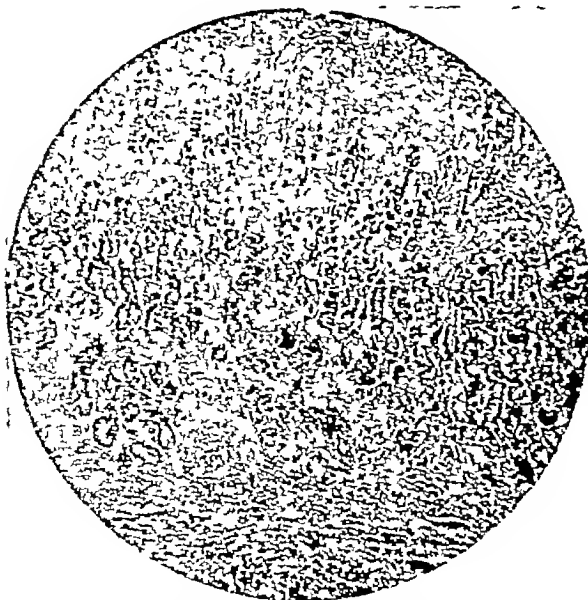


Fig. 4 Photomicrograph of hemorrhagic spot in dog's stomach showing extensive hemorrhage into both mucosa and submucosa with coagulation and necrosis of superficial epithelium.

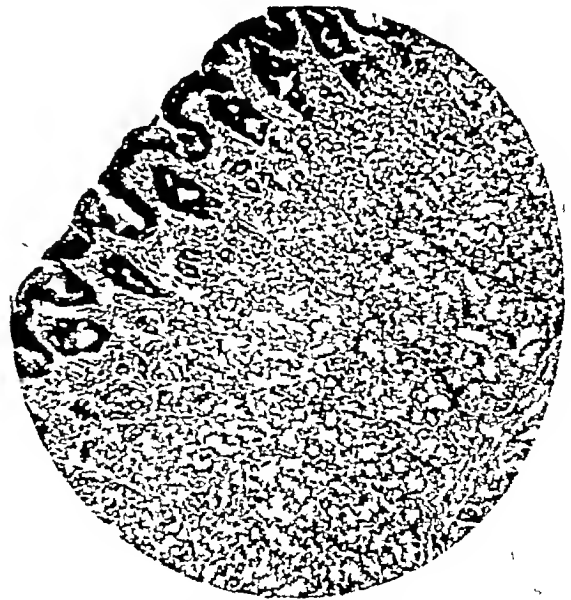


Fig. 4a Photomicrograph of dog's stomach through area not showing pigment spots.

tize the mucosa and produce minor changes which might be misinterpreted as being of importance, or the explanation of the patient's symptoms

One of the most perplexing problems confronting the physician is that of unexplained upper intestinal hemorrhage, in which there is either hematemesis, a tarry stool, or both and in which all studies, including a gastro-intestinal series, are negative. It is not surprising that an effort should have been made to attribute these hemorrhages to superficial ulcerations of the gastric mucosa, which are not visible by X-ray. While not denying that this may be the answer, still in our experience nothing has ever been seen gastroscopically which we felt could explain this type of bleeding. It is true that hemorrhagic or pigment spots were seen in four cases out of twelve of unexplained hemorrhage. However, they have been seen so often in normal individuals, and in other patients who have no evidence of bleeding, that one would hardly feel justified in concluding that the hemorrhage was due to their presence.

The production of these spots in the experimental animal merely by aspiration further confirms the impression that they can be the result of trauma, and they can be duplicated in the dog at will. The spots produced in the dog were hemorrhagic areas with necrosis of tissue within the mucosa and in some instances loss of surface epithelium. This was also the case in the patient, who died of a pulmonary embolism (Case 2). This observation might well justify the

conception of a possible relationship between these spots and the genesis of ulcer. It would not be difficult to imagine that the "corrosive action" of the gastric juices bathing an erosion, or an injured mucosa, might produce the usual chronic, punched-out ulcer. However, our observations lead to the conclusion that no such relationship exists, and that these spots are merely localized hemorrhagic areas which disappear spontaneously within a few days, leaving no trace of their presence.

Wide differences of opinion have been expressed as to the incidence of chronic gastritis. It was pointed out in an earlier publication (11) that failure to take into consideration the factor of inflation might account for some of these discrepancies. This study would indicate that failure to take into consideration the factor of trauma, either due to aspiration or to the passage of the gastroscope, might likewise account for the high incidence of gastric disease as reported from some clinics in this country.

CONCLUSIONS

- 1 Hemorrhagic or pigment spots in the gastric mucosa can be produced by aspiration of the stomach
- 2 They may occur in healthy individuals
- 3 Their relationship to peptic ulcer is questionable
- 4 They probably have no clinical significance
- 5 The factor of trauma should be carefully considered in the interpretation of gastroscopic findings

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Generalized Pruritus Due To Carcinoma of the Stomach and Cured by Gastrectomy

By

LEONARD CARDON, M D *
CHICAGO ILLINOIS

SYSTEMIC diseases known to be frequently associated with generalized itching of the skin include diabetes mellitus, jaundice, and the lymphoblastomas, especially Hodgkin's disease. Visceral carcinoma (not associated with jaundice) as a cause of generalized itching is mentioned in the literature, but specific case reports were not found. Nor is mention made of cure of the itching by the surgical removal of the carcinoma. Personal communication with several gastroenterologists, internists, and surgeons of long experience reveals that they have never seen nor heard of this association. For this reason, it is felt that the

report of a case of intractable generalized pruritus of three years' duration in which a carcinoma of the stomach was discovered and in which the itching of the skin was cured by successful surgical removal of the carcinoma may be of interest.

CASE REPORT

M P, a Jewish male, 89 years of age, was admitted to the Mt Sinai Hospital of Chicago on 12-29-41 complaining of generalized itching of the skin of three years' duration, insomnia, and rheumatic pains in the small joints of the hands. The itching was the predominant symptom and its intensity was such that it made the patient's existence miserable. It was often necessary for the patient to ingest 3 grains each of amytal and nembutal, one grain of pheno-

*Associate in Medicine Northwestern University Medical School
Attending Physician Cook County Hospital Associate Attending Physician Mt Sinai Hospital of Chicago

barbital, and 10 grains of aspirin all in one dose at bedtime in order to sleep. This was varied on occasion by taking 9 grains of allonal at a time or 3 grains of nembutal two or three times a night in a desperate effort to obtain some relief from the itching and a period of undisturbed sleep. Pantopon, morphine, codeine, chloral hydrate and many other sedatives had all been tried at one time or another. He had been under continuous expert dermatological supervision throughout his illness. The list of local applications which had been tried included calamine lotion (with and without menthol and phenol), bismuth cream (with and without menthol and phenol), starch lotion, alcohol rubs, wet packs of aluminum subacetate, 2 per cent ichthylol, Lassar's paste, boric acid ointment, mild salicylic acid ointment (1 per cent), tar paste, cod liver oil ointment, ointment containing the male sex hormone testosterone, contrast baths, Unna's boots, gel casts, paraffin boots, exposure to ultraviolet and infrared rays, and diathermy treatment. By parenteral injection he had received calcium gluconate, strontium bromide, splenic extract, liver extract, thiamine chloride, nicotinic acid, and ascorbic acid. By mouth he had received calcium salt, large doses of Vitamins A, B, C, and D, and dilute hydrochloric acid. He had received testosterone in single 25 mg daily doses, at first by subcutaneous injection and then by mouth, in several series of twenty doses each. Digitalis, one and one-half grains daily, had been taken because of a tendency to ankle edema on exertion, but the itching had not been relieved when this medication was discontinued. Trial periods in which all sedatives had been discontinued also failed to relieve the itching.

Physical examination revealed a small, frail man, haggard but not acutely ill, and in full possession of his mental faculties. The temperature was 98.6 F, pulse 72, respirations 20, and blood pressure 130/80. The hair was sparse but soft. There was an arcus senilis and some opacity of the media in both eyes, the pupils were normal. The few remaining teeth were carious. The tonsils were present. The thyroid gland was not palpable. There was a soft systolic murmur at the cardiac apex and a rough systolic murmur in the right second interspace and all along the right sternal margin, transmitted into the neck vessel, there was no palpable thrill. The lungs were negative. A firm tender mass palpated in the right epigastrium was interpreted as liver. There were arthritic deformities of the hands and fingers. The radial arteries were extensively sclerotic. Rectal examination was negative. The skin was smooth and soft throughout and presented no rash, excoriations, atrophies, or other abnormalities. A tentative entrance diagnosis was made of somatic senility, generalized ("idiopathic" senile) pruritus, chronic arthritis, and arteriosclerotic heart disease with sclerosis of the aortic leaflets.

The urine had a specific gravity up to 1.030 and contained no sugar (although a slight reduction of Benedict's solution occurred during the time he was taking chloral hydrate), or other abnormalities. A totally unexpected finding in the blood (because of the absence of any noticeable pallor) was a hemoglobin of 43 per cent. The red blood count was 4,120,000 and the white count 11,650. Stab forms 3, segmented neutrophils 65, small lymphocytes 27, and monocytes 5. The bleeding time was 5 minutes, coagulation time 7 minutes, and the platelets numbered 255,000. The blood citramic acid was 0.95 mg/100 cc and the prothrombin time 93 per cent of normal. The blood type was 3 and the Kahn negative. The blood sugar was 90, urea nitrogen 15, non-protein nitrogen 30, cholesterol 167, calcium 10.6, phosphorus 2.8, phosphatase 2.0, and icterus index 6.0. Stools revealed 3 plus occult blood on two occasions. Ewald test meal was not done. The BMR was -4.0 and 0.0%. The EKG was within normal limits for the patient's age.

On 1-9-42 X-ray revealed a large carcinoma of the pre-antral region of the stomach. Blood transfusions and iron

by mouth brought the hemoglobin up to 64.2 per cent but the itching was not relieved. Thyroid extract by mouth was of no avail.

On 1-30-42 under intra-tracheal cyclopropane anesthesia (Dr Sholtz), laparotomy was performed by Dr Alfred Strauss. A large but freely movable and operable carcinoma of the stomach was found. No metastatic lesions were visible. Gastrectomy with the removal of 60 per cent of the stomach was performed and a Polya anastomosis established. The histological report of the excised tumor (Dr Israel Davidsohn) was "ulcerating, infiltrating papillary adenocarcinoma of the stomach."

Post-operatively, blood transfusions and oxygen were used freely. Recovery from the operation was quite uneventful except for the development of a collapse and pneumonitis of the right lower pulmonary lobe of four days' duration.

A new situation was introduced in that the patient's old habit of rumination now resulted in regurgitation of bile and the constant presence of a bitter taste in the mouth, which depressed the patient considerably. However, the pruritus disappeared with the emergence of the patient from the anesthesia. He left the hospital on 2-24-42 weighing 90 lbs, still free of itching.

He was readmitted to the hospital 3-6-42 with the complaints of regurgitation of food and bile, weight loss, weakness, and mental depression. He weighed 82½ lbs. The blood hemoglobin was 82 per cent and the red count 4,210,000. X-ray of the stomach revealed a well functioning anastomosis with no evidence of local recurrence of the malignant lesion. Frequent lavage of the stomach was resorted to. The patient was taught to pass a Levine tube and lavage the stomach himself. He was discharged from the hospital on 4-1-42 weighing 84½ lbs. There had been no itching since the operation.

The patient was seen again on 4-25-42. He was still markedly depressed about the regurgitation of bile and the bitter taste in his mouth. His weight had dropped to 72½ lbs. From this date on, however, improvement was slow but steady, necessity for gastric lavage diminished constantly, appetite improved, the patient gained weight steadily, and his interest in life revived. At the present writing (9-1-42) he weighs over 100 lbs, is cheerful and happy, putters about at light repairs and cabinet work in his home, and is writing an autobiography. He has learned that ingestion of hot spicy food overcomes the desire to regurgitate his food and he eats "hot dogs" with mustard two or three times daily. Lavage of the stomach is not necessary. He still takes nembutal, grains one and one-half, at bedtime for sleep. There has been no itching since the operation, a period now of twelve months.

COMMENT

The occasional association of generalized pruritus with visceral carcinoma is mentioned by Ormsby (1), Hemmeter (2), Sulzberger (3), Wright (4) and Goldsmith (5). The mechanism by which internal carcinoma can cause itching of the skin is a matter of speculation. The fact that in the case here reported the itching was immediately relieved with the removal of the primary malignancy would seem to argue for some toxic metabolic or degenerative product of the carcinoma per se circulating in the blood stream as an intermediary in this association.

Because of the patient's advanced age and lack of symptoms directly referable to the gastric lesion it is doubtful whether operation would have been considered under ordinary circumstances. Except for the pruritus the patient was leading a relatively comfortable existence and digesting his food without trouble. The intractable itching which made his life insupport-

able was the sole but sufficient indication for assuming the risk and morbidity of gastrectomy, since this procedure alone seemed to offer any hope for the relief of this distressing symptom. It was felt also, that if the itching was secondary to the carcinoma, then the latter had been existent for three years, and this argued that it might be of the slowly growing lesions common in those of advanced age which although locally extensive are often circumscribed, without metastases, and resectable.

Successful gastrectomy for gastric malignancy with the removal of 60 per cent of the stomach in a man 89 years of age is itself worthy of note.

SUMMARY AND CONCLUSIONS

1 A case of generalized pruritus of the skin due

to carcinoma of the stomach and cured by gastrectomy is reported.

2 "Idiopathic" and "senile" pruritus in a certain (unknown) percentage of cases may be a manifestation of silent visceral carcinoma.

3 Under proper circumstances gastrectomy for gastric malignancy may be a feasible procedure even in patients of advanced age.

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Thiamine Influence Upon Laxative Action*

By

S LOEWE, IDA LOEWE

and

ROBERT KNOX, JR

NEW YORK, NEW YORK

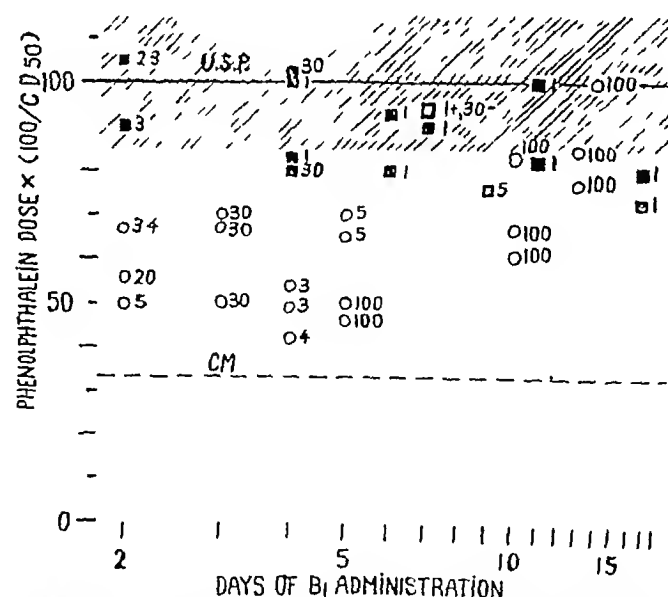
THE animal experiments (1, 2), by showing that the beneficial action of thiamine upon the intestine appears to be limited to hypothyroidism, justifies the use of thiamine in conditions having this etiology. There is however, a tendency to use thiamine also in combination with cathartics. The question whether there is a synergism between thiamine and laxatives, may be answered by experiments in the rhesus monkey, the only species suitable for measuring the effectiveness of cathartic drugs (3, 4).

This report is based upon 443 experiments in rhesus monkeys†. Phenolphthalein was chosen as a test substance because the response of the monkey to this drug is well defined and an assay method is available (4, 5, 6). Eleven adult monkeys of either sex were calibrated with a standard USP phenolphthalein in 14 to 65 (average 38, total 413) experiments to determine the individual oral threshold cathartic dose (CD_{50}). In 25 experiments the same monkeys were fed varying fractions of the individual CD_{50} and at the same time daily doses of one to 100 mg/kg of thiamine hydrochloride were administered in two equal doses in 8 hours. The period of thiamine treatment extended over the day the phenolphthalein was administered, the subsequent day, and a varying number of preceding days. The care of the monkeys, diet, administration of the drugs, recording and evaluation of the laxative effect were described elsewhere (4, 5, 6, 7).

A survey of the experiments is given in graph 1, representing the distribution of positive and negative results in relation to the phenolphthalein dose and to the period and dosage of the thiamine treatment. When the individual sensitivity to the laxative changed in the course of the long calibration period, the test dose given in the thiamine period was referred to the CD_{50} of the pre- and that of the recalibration period.

Hence, the number of entries in the graph is higher than the number of experiments.

In the evaluation proper, these variations in sensitivity did not interfere with the result since it is the express purpose of the "procedure of approximation" (5, 6, 7) to take them into consideration. By approxi-



■ = experiments with, ○ = experiments without laxative effect — Figure at individual experiment = thiamine doses in mg/kg per day

mation from a total of 40 values of maximum and minimum potency obtained in the 25 synergism experiments the potency of phenolphthalein was found to be 1.175 ± 0.20 as referred to the potency value 1.0 of phenolphthalein in the calibration periods. In other words, the synergistic increase in potency of phenolphthalein effected by all kinds of thiamine treatment

*From the Laboratory of the Medical Division The Montefiore Hospital New York N Y
†Sponsored by F&L Inc Brooklyn N Y

increased to about 18 per cent with a coefficient of variation of ± 17 .

In the routine bioassay of cathartics in rhesus monkeys the range of variation is about ± 10 per cent. It may be assumed to be greater in experiments of the type presented here because both pre- and retention experiments are separated from the test experiment by greater intervals of time: the former by the thiamine pre-treatment period, the latter by a period of safety required to avoid possible persistence of the drug effect. An even wider range than ± 17 per cent was obtained by conducting additional experiments with phenolphthalein doses higher than the (10).

(17) The mean value of potency from experiments with widely varying thiamine treatment. As can be seen from the graph there is, however, no convincing indication that the effectiveness of phenolphthalein was significantly increased by prolonged thiamine treatment or by higher thiamine dosage. To the contrary, if there was any synergistic influence in relation to the thiamine dosage, it was rather in the range of the smaller doses—10 to 100 mg/kg daily—considerably greater than a dosage of maintenance or of complete substitution. That these large doses failed to increase the effectiveness of the laxative indicates in itself that diet, food intake and state of health of the animals were of no great importance. Actually no more convincing synergistic effect of thiamine than in normal animals was seen in monkeys with a fatal disease (usually tuberculosis), with lower sensitivity to the laxative or with decreasing body weight—three possible signs of hypothyroidism. For

practical purposes the insignificance of the synergism attained in these thiamine experiments can best be emphasized by contrasting it with the incomparably greater increase in effectiveness, namely by 200 per cent which is readily obtained by replacing USP phenolphthalein by commercial—so called "yellow"—phenolphthalein.

Since in some of these experiments any indication of enhanced intestinal activity was absent even after thiamine doses several hundred times higher than those in therapeutic use, their outcome is direct evidence that thiamine is useless as a laxative and has no place in the therapy of constipation "unless it is the direct result of a deficiency" (8).

SUMMARY

Experiments in the rhesus monkey give no support to the assumption of a synergistic influence of Vitamin B₁ upon laxative action. Daily doses from 10 to 100 mg/kg thiamine hydrochloride, orally administered over periods of 2 to 17 days, did not significantly increase the effectiveness of a laxative (phenolphthalein). The average increase in effectiveness in 25 experiments was 18 per cent with a variation of ± 17 per cent.

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Liver Function Tests in the Aged

(The Serum Cholesterol Partition, Bromsulphalein, Cephalin-Flocculation and Oral and Intravenous Hippuric Acid Tests)*

By

HENRY A. RAFSKY, M.D., F.A.C.P.

and

BERNARD NEWMAN, B.S., CHE

NEW YORK, NEW YORK

In a previous article we reported the fact that in studying the cholesterol partition in normal individuals past sixty years of age we found that a majority of the subjects had a total serum cholesterol concentration exceeding 200 mg per cent, with more than forty per cent existing as the free sterol. These findings prompted us to make a study of various liver function tests in a group of so-called normal individuals within this same age group. To the best of our knowledge no such report has as yet been published.

EXPERIMENTAL STUDY

The subjects chosen for this study comprised twenty-three males and twenty-seven females. All were ambulatory and were housed in the "Home division" of the institution, and were on the normal institutional

diet. They did not present any clinical evidence of disease including hypertension, and were as normal as any group of similar age could be.

The tests selected for this investigation were Hanger's Cephalin-Cholesterol Flocculation Test (2), Rosenthal's Bromsulphalein Test (3), the Serum Cholesterol Partition, and both the oral and intravenous Hippuric Acid Tests (4, 5). The Rose Bengal Test was not done because it was not feasible in these individuals. The van den Bergh, the Icteric Index and the Galactose Tolerance Tests, were not done because none of the subjects showed evidence of jaundice.

The Cephalin-Flocculation Test was performed as follows. The cephalin-cholesterol reagent was made up according to Hanger's original report (2), except that as was suggested by Mateer (6), the cephalin was allowed to ripen for about six weeks to a brown

*Presented at the Home of the Daughters of the American Revolution, New York, N. Y., June 1941.

color and slightly gummy consistency. Venous blood was withdrawn and allowed to clot. The serum was removed and centrifuged to free it of red cells. In a centrifuge tube were placed 0.2 cc of the serum, 4.0 cc of physiological saline solution, and 1.0 cc of the cephalin-cholesterol reagent. After a thorough shaking, the mixture was plugged with cotton, and was kept undisturbed at room temperature for forty-eight hours, at the end of which time the amount of flocculation or precipitation was noted. With normal sera, the cephalin-cholesterol emulsion remains as a stable homogeneous suspension, but with sera from individuals showing a diffuse hepatitis, the lipid ma-

terial tends to come out of suspension, and collects at the bottom of the tube. In sixteen, or thirty-two per cent of the subjects studied, flocculation, or evidence of disease of the liver parenchyma was present.

The cholesterol partition was determined according to the method of Bloo and Knudson (7), as described by Todd and Sanford (8). The maximum normal limit for total serum cholesterol as given by several investigators (8, 9, 10, 11), has been stated to be 200 mgm per cent, with a maximum free cholesterol of forty per cent. We found thirty-three, or sixty-six per cent of our subjects to show a total serum cholesterol concentration in excess of 200 mgm per cent, while the

TABLE I
Results of liver function tests

Case No	Sex	Age	Ceph. flocc.	Icterusulphalein		Cholesterol		Hippuric Acid	
				5 Min	30 Min	Total	% Free	Ornl	1 V
1	M	63	0	22%	0	217	30	2.9	0.89
2	F	74	0	23%	trace	193	67	3.4	1.1
3	M	79	0	31%	0	230	57	2.7	0.88
4	F	72	1 plus	29%	trace	310	40	3.0	1.3
5	F	69	0	19%	0	197	48	3.2	1.0
6	M	70	0	30%	5%	236	35	2.9	0.87
7	F	79	1-plus	34%	trace	178	56	2.2	0.79
8	M	81	0	29%	0	248	63	3.0	0.86
9	M	76	0	38%	trace	235	10	3.2	1.0
10	F	83	1 plus	48%	10%	310	45	3.6	0.97
11	F	74	0	39%	0	320	52	3.5	1.2
12	F	50	0	26%	0	229	40	2.0	0.93
13	F	76	0	52%	14%	200	64	2.5	1.0
14	F	68	0	27%	0	249	28	3.4	0.91
15	M	74	0	31%	0	231	25	2.0	0.88
16	M	78	0	40%	11%	340	46	3.6	0.8
17	M	79	0	32%	trace	244	47	2.0	1.0
18	F	73	1 plus	20%	2%	220	26	2.9	1.07
19	F	83	1 plus	33%	8%	301	51	3.3	0.94
20	F	50	0	10%	0	155	32	3.0	1.09
21	F	72	0	28%	trace	230	27	2.8	0.95
22	F	74	0	30%	3%	313	52	2.7	0.80
23	F	60	1 plus	25%	trace	230	17	2.9	0.90
24	M	77	0	10%	2%	280	27	2.6	0.07
25	F	76	0	26%	trace	188	42	3.1	1.07
26	M	70	1 plus	27%	6%	279	34	2.4	1.05
27	F	72	0	31%	0	190	21	3.2	0.96
28	F	88	0	29%	0	216	30	2.0	1.01
29	M	76	0	30%	trace	288	34	3.1	0.99
30	M	66	1-plus	22%	0	180	16	2.8	0.79
31	M	79	2 plus	28%	7%	290	52	2.5	0.69
32	F	85	0	30%	0	200	40	3.0	1.08
33	M	93	1-plus	41%	16%	248	53	2.9	0.82
34	M	81	0	26%	trace	219	25	3.1	1.2
35	F	78	1 plus	22%	trace	187	27	2.7	0.70
36	M	66	0	10%	0	194	30	3.2	1.02
37	F	69	0	33%	trace	227	36	2.7	0.82
38	M	71	1 plus	26%	0%	312	49	3.3	1.2
39	F	78	0	28%	trace	168	25	2.8	1.1
40	F	66	1 plus	20%	0	202	50	3.1	0.87
41	F	68	0	34%	13%	290	57	2.0	0.62
42	M	83	0	10%	0	202	40	3.3	1.20
43	F	76	0	28%	6%	179	40	3.6	0.81
44	M	83	1-plus	24%	9%	231	43	4.0	0.60
45	M	77	0	17%	0	185	16	2.0	1.0
46	F	73	1 plus	30%	trace	246	48	2.8	0.6
47	M	78	0	18%	0	197	21	3.5	0.88
48	M	65	0	27%	0	233	34	2.8	1.2
49	M	85	0	29%	trace	277	37	3.8	0.92
50	F	65	1 plus	36%	10%	274	59	2.6	0.61

free cholesterol was more than forty per cent in twenty-two, or forty-four per cent of the subjects. Thirty-two per cent showed an increase in both the total and the free cholesterol.

The bromsulphalein test was performed as follows. A specimen of blood was withdrawn from the median basilic vein and permitted to clot. This served as the specimen for the other tests as well as a control. Through the same needle an amount of bromsulphalein equivalent to 50 mgm per kilo of body weight was administered. At the end of five minutes and at the end of thirty minutes, specimens of blood were withdrawn from the opposite arm and allowed to clot. The serum was then drawn off from each specimen. To the same volume of each was added a sufficient amount of forty per cent sodium hydroxide solution

TABLE II

Percentage abnormal for the various function tests

Per Cent Abnormal	Ceph Lin Flocculation	Brom sulph alein	Cholesterol		Hippuric Acid	
			Total	Free	Oral	Intravenous
	32	26	66	44	6	24

to bring out the maximum color of the dye (if present). All were brought up to the same volume with physiological salt solution and comparisons were made with an alkaline standard solution of the dye in a spectrophotometer. With this test, the normal variations are from twenty to forty per cent with an average of thirty-five per cent in the five minute specimen, while the thirty minute sample should show either nothing or a slight unreadable trace (12). As can be seen from the tables, thirteen, or twenty-six per cent of the subjects showed definite dye retention, since we regarded as abnormal, anything over five per cent in the thirty minute sample.

The oral hippuric acid test was performed by giving the fasting subject 6.0 gm of sodium benzoate U.S.P. dissolved in an ounce of water and flavored with a drop of oil of peppermint. No nausea was encountered when the oil of peppermint was used to disguise the taste. The urine was collected at hourly intervals for a total of four hours. The specimens were concentrated to half their volumes by boiling, and were cooled to room temperature. The urine was then made strongly acid to congo red by means of a few cc of concentrated hydrochloric acid and placed in the refrigerator for about an hour. The precipitated crystals of hippuric acid were then filtered off, air dried and weighed to the second decimal place. A correction of 0.55 gms was made for each 100 cc of urine according to the recent work of Weichselbaum and Probst (13), and this was added to the weight of hippuric acid. Using this procedure, an excretion of less than 2.5 gm of hippuric acid in four hours is considered evidence of liver disease. Six of our subjects or twelve per cent excreted less than this amount during the specified time.

The intravenous hippuric acid test was performed by administering, intravenously, 10 cc of a twenty per cent solution of sodium benzoate. It was found that when the injection was made extremely slowly, taking about ten minutes, no untoward effects were noted. The urine was collected at the end of one

hour, and the amount of hippuric acid estimated as in the oral procedure. After intravenous administration of 2.0 gm of sodium benzoate, more than 0.85 gm, should appear in the urine in one hour. Twelve subjects, or twenty-four per cent of the individuals under investigation excreted less than this amount in the specified time.

COMMENT

A total of 250 liver function tests were performed in a group of fifty normal individuals over sixty years of age. In forty-three, or eighty-six per cent of these subjects, at least one of the tests showed evidence of liver dysfunction, according to the usually accepted standards. Thirteen subjects, or twenty-six per cent, showed hepatic impairment in two of the tests. One subject, or two per cent, showed poor liver function in three of the tests used, while in thirteen, or twenty-six per cent, four or more of the tests were abnormal. In this connection, it might be stated that according to Mateer (14) the ripening process employed, in the cholesterol-cephalin flocculation tests increases the sensitivity of the cephalin. This may possibly account for the high percentage of abnormalities obtained, since Pohle and Stewart (15) performed flocculation reactions on 284 normal younger individuals, and in no instance did significant flocculation occur. They did this without preliminary ripening of the cephalin.

The results observed in this study bring up the question as to the significance of the comparatively large percentage of abnormal results in these apparently normal aged individuals. Various liver function studies have been made by different observers (14, 16, 17) using comparatively young healthy individuals as controls. In only one report thus far published, that of Paulson and Wiler (18), were hospitalized patients above the age of sixty used as controls. These observers studied eleven patients above this age, eight with suspected liver metastasis, and three in whom no liver disease was suspected. One of the latter patients had auricular fibrillation with multiple emboli, and the other two had pneumonia. But no study reported thus far, as was stated in the beginning of this paper, was made of the various liver function tests in normal subjects past sixty years of age. It is conceded that with advancing years, certain changes take place within the system. But it is also true that these changes may be perfectly compatible with normalcy for this age distribution. Our subjects were as normal as any individual in this age group could be, insofar as activity, health habits and daily routine were concerned. Some were employed about the institution as messengers, gatekeepers and book-binders; others again were active as supervisors, carpenters, tailors, librarians, etc., but all were up and about. It therefore seems to follow that abnormal results of liver function tests may be encountered in apparently healthy subjects above sixty years of age.

SUMMARY

1. Various liver function tests were performed on normal individuals past sixty years of age.

2. In eighty-six per cent of these subjects, at least one of the tests showed evidence of liver dysfunction.

3. Abnormal results of liver function tests may be encountered in apparently healthy subjects above sixty years of age.

The authors express their appreciation to Dr. Samuel Seidenberg for his cooperation in this study.

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Duodenal Tube Biliary Tract Drainage

A 25 year "follow-up" report on Anna Ingber Penn, the first person to undergo treatment by this method

By

B B VINCENT LYON, M D, Sc D
PHILADELPHIA PENNSYLVANIA

THIS is a 25 year 'follow-up' report upon Anna Ingber. She first came under my observation in the spring of 1917.

I am aware of the temerity of attempting to make such a report when I recall the admonition of my revered teacher at Johns Hopkins, Sir William Osler "May God protect us," said Osler, "from the doctor who reports just one case!"

I should explain, therefore, that Anna Ingber was the first person to become a human 'guinea pig' in order to test out a new method, which, to some extent, has served to influence the diagnosis and therapy of biliary tract diseases. This method was also to test out the validity of an observation, concealed in a footnote, of the late Samuel J Meltzer (1).

Dr Meltzer, then of the Rockefeller Institute, in his experiments on dogs, had observed that if bile was not flowing into the exposed duodenum he could readily make it do so by douching the mucosa with a solution of magnesium sulfate*. He attributed this to the relaxing effect that the magnesium ion exerted upon unstriated muscle.

In this footnote he also stated that he believed that the duodenal tube† might become a useful instrument with which to recover human bile. Up to 1917, bile from the liver, the hepatic ducts, and from the gall bladder had rarely been recovered for study, and never for treatment, except by the abdominal surgeon, or at autopsy by the pathologist.

Although Meltzer did not specifically mention it, his footnote suggested to me that, if a proper duodenal tube technique for recovering bile could be perfected, this method might give us an opportunity to study the respective biles and thereby might possess diagnostic value in liver and gall bladder diseases. Further, I felt that it might also have therapeutic value in draining, externally, pathologic bile from the sick human

being. But it required nearly 10 years to prove this to the satisfaction of our profession.

It is possible that the reason Meltzer, in his article, did not more fully develop the potential diagnostic and therapeutic implications was because his main thesis was an attempt to further bulwark his Law of Contrary Innervation, as it applied to the biliary system. He believed that as the sphincter of Oddi relaxed the gall bladder should contract, and vice versa.

I have always considered myself fortunate that I had, for seven years,* 'leadied' myself in duodenal intubation, and doubly so, because, shortly after reading Dr Meltzer's footnote, I found a suitable subject in Jefferson Hospital upon whom I might experiment.

This patient was Anna Ingber, then not quite seventeen, an Austrian born Jewess, who 4 years later became the wife of Frank Penn, a window cleaner, and subsequently bore him six children, by five pregnancies, within a space of 12 years.

Anna was not what might be called an 'easy' case upon whom to try a new therapeutic experiment. But I was rather glad of it. I felt that if I could get that child well, and, under the circumstances keep her well, this new method might become a useful agency for many persons ill with biliary tract and other associated diseases.

In 1917 Anna was indeed very sick in the women's surgical ward. She had an obstructive form of jaundice, despite the fact that she had already undergone four operations on her biliary tract within less than 3 years. In addition she had had six other admissions to the medical and surgical service of Jefferson Hospital, altogether totalling 237 days. To this must be added 123 days spent in the Methodist Hospital of Philadelphia, where she underwent, for the first time, duodenal tube biliary drainage, or a total of 360 hospital days.

*Consult 2nd footnote in Reference 1.

†Discovered and developed independently by Drs Max Einhorn and Maurice Gross both of New York in 1900-1910.

*The author established the first stomach clinic in Philadelphia at the German Hospital in 1910 and the second one at Jefferson Hospital in 1912.

It was fortunate for Anna that the experiment worked. The surgeons, Professor John H. Gibbon and his Associate Professor Duncan Despard, of Jefferson Medical College, had found each succeeding operation technically more difficult because of progressive adhesions which obscured the usual surgical landmarks.

The chronology of the aforesaid 12 admissions, with the diagnoses made by the various services, between 1912 and 1917, is summarized as follows:

1. Patient (C 1848) admitted to Jefferson Hospital, service of Dr. John H. Gibbon on October 5, 1912. Discharged on October 31, 1912, with a diagnosis of empyema of the gall bladder. Cholecystostomy.

Chief Complaint Abdominal pain, in upper right quadrant.

Family History Father and mother, living and well. 3 sisters living and well. 1 sister has pulmonary tuberculosis. No history of heart, kidney or malignant disease. No history of jaundice in family.

Previous History Measles and helminthiasis. Patient states that as a child in Austria she used to pass white, round worms, 6 to 12 inches long. "Some would crawl out of my mouth." She used to take krait for them. During this time she had frequent abdominal cramps. At 10 years of age she began to have attacks of upper right quadrant pain periodically.

Present Illness At 12 years, pain became severe, constant, radiating around right costal margin to back. Three days before admission she had chills, sweats, vomiting, mild jaundice, and was slightly delirious.

Physical Examination Recti rigid, right plus. Bulging mass in right mid-clavicular line, midway between right costal margin and umbilicus.

Operation Dr. Despard. Cholecystostomy. Much pus and thick mucus aspirated from markedly distended gall bladder. Pure culture of *B. pyocyaneus*. Recovery uneventful. Highest temperature was 103 on admission, reached normal on 17 p.o. day. Patient discharged, cured on 26 p.o. day. Diagnosis: Empyema of gall bladder.

2. Patient (C 3291) admitted to service of Dr. Fielding Lewis on Jan. 6, 1913. Discharged Jan. 11, 1913. Tonsillectomy, adenectomy.

3. Patient (D 6353) admitted to surgical service of Dr. Gibbon on May 13, 1914. Discharged on June 8, 1914. See previous admission for past history.

Present Illness Since first admission patient has had recurrences of upper right quadrant pain and jaundice. Day before admission had violent, colicky pain, chills and fever, persistent vomiting. Jaundice. Mass size of lemon in U.R.Q. tender.

Operation Dr. Despard. Cholecystectomy, choledochostomy. Stones found in markedly distended gall bladder and in common duct were removed. Free flow of pus from common duct. Culture again grew out *B. pyocyaneus*. The choledochostomy tube was dislodged a week later and several stones fell out. Patient was discharged with sinus still draining.

4. Patient (E 500) admitted to surgical service on June 23, 1914. Discharged on July 16, 1914.

Present Illness Since last admission patient has had recurrence of U.R.Q. pain, nausea and vomiting. Occasional chill, fever and jaundice.

*This was in the early and experimental period of biliary surgery. Diagnoses could not be made so accurately and fully. X-ray machines and methods were cruder. Biliary drainage and cholecystography had not been discovered. Liver function tests had not yet been developed. Clinical diagnosis was limited.

Operation Dr. Despard. Surgical closure of persistently draining sinus. Patient discharged on July 16, 1914.

5. Patient (E 6395) admitted to surgical service on April 16, 1915. She states that during the past year she has had recurrences of pain, nausea, vomiting, chilliness and mild jaundice. Also, weakness in lumbar region. Pain continues, at times, day and night. Patient appears very nervous, bordering on hysteria. Superficial and deep tenderness over scar. Leucocyte count, 16,000 on 4-17, 17,800 on 4-20-15.

Surgical service considered it unwise to re-operate at this time. Patient was discharged on April 22, 1915. Diagnosis: Cholangitis and hysteria.

6. Patient (E 7308) readmitted to surgical service of Dr. Gibbon on May 30, 1915. She states that after her last discharge, there was prompt recurrence of symptoms described on previous admission, but with increased jaundice. Leucocyte count on admission was 28,000, rising to 31,000 on the following day.

Operation Dr. Despard, after aspiration of brownish sero-purulent fluid from the common duct removed several stones. A second cholecystostomy was done, after partial release of extensive adhesions. Patient was discharged on July 10, 1915.

This operation, too, failed in yielding permanent relief.

7. Patient (F 1454) admitted to the medical service of Prof. Thomas McCrae, on August 12, 1915 for observation. On this admission a culture of bile, recovered from the duodenum, again grew out *B. pyocyaneus*. Patient was discharged on August 26 with a diagnosis of peri-gastric adhesions.

8. Patient (F 3208) again admitted for observation on the service of Dr. McCrae on October 27, 1915. Her symptoms had continued much as before. Discharged on November 18, 1915, with a diagnosis of abdominal adhesions.

9. Patient (F 6778), still complaining of epigastric and right hypochondriac pain, nausea and vomiting, was readmitted to the surgical service of Prof. Gibbon on April 15, 1916, and discharged on April 22 with a diagnosis of abdominal adhesions.

10. Patient (G 707) continued to suffer further attacks of pain and was once more readmitted to the medical service of Prof. McCrae on July 3, 1916, and was discharged on July 15 with a diagnosis of surgical neurasthenia.

11. Patient (G 4879) was admitted for the eleventh time to Jefferson Hospital, this time to the surgical service of Dr. Gibbon, on January 9, 1917. This time she was very sick. She had severe paroxysmal pain in the right upper abdomen, radiating around the costal margin to the back, nausea, chills and fever. Her jaundice had deepened and was accompanied by intense pruritus. Her stools were light yellow to clay color. Her urine a dark brown and stained the toilet bowl.

At this time the writer was invited to see Anna in consultation with the surgical division. By duodenal tube culture of her bile I again recovered *B. pyocyaneus*, this time with *B. coli*. Vaccination with these bacteria was begun. She was not discharged until March 5, 1917, with a diagnosis of hepatocholangitis obstructive.

*These diagnoses were certainly only partially correct for the patient insists that before each of these several readmissions she had recurrent pain and was mildly but definitely jaundiced.

The patient soon relapsed, but refused to reenter Jefferson Hospital, where she was considered to have 'hospitalitis'. With the approval of Drs Gibbon, Despard and McCiae, Anna was admitted on April 9, 1917, to the Methodist Hospital, under my service.

I had just read Dr Meltzer's article and was impressed by the potentialities suggested in his second footnote. So, for the first time in medical history, Anna underwent duodenal tube treatment for a biliary tract obstruction. And with gratifying results.

As soon as I had succeeded in unblocking her obstructed common duct she immediately felt better. Her fever lessened, her leucocytosis diminished, her jaundice and itching gradually subsided. Cultures once more grew out *B. proteus*, and a fresh vaccine was used.

She was discharged on July 31, 1917, with the following diagnosis: Relapsing hepato-cholangitis, infecting agents, *B. proteus*, *B. coli*, and *Staph. aureus*, upper right quadrant adhesions, common duct sand, probable cirrhotic changes in liver.

She was told to report to my out-patient stomach clinic at Jefferson Hospital for follow-up care. I sailed for France in September, with Navy Base Hospital 5, and the larger number of her follow-up drainages were given her by Dr Henry J. Baile. On my return Anna was well on the way to better health.

The technique of de jaundicing Anna and her total medical care at the Methodist Hospital has been fully reported elsewhere and need not be repeated here (2, 3).

When I last reviewed this case (4), I stated that, in addition to her four operations, Anna had required four months treatment in the Methodist Hospital, and two years of follow-up care. This brought her up to 1920. She then remained remarkably well for a number of years, save for a few minor relapses that taught us many things.

Up to and including 1924, Anna had received frequent biliary drainages being asked to report to the Clinic for this purpose at intervals not to exceed three weeks. At first her cooperation was not too good. She hated to come so often, but she soon learned the hard way. By the end of 1924 she herself was able to detect the onset of the prodromal symptoms that ushered in a recurrent hepatocholangitis, symptoms which she had found were best relieved by biliary drainage. She became a good subject for teaching medical students duodenal tube technique, and biliary drainage therapy. She was shown annually in the Amphitheatre before the Junior and Senior classes for a number of years, later on biannually. Also, between 1930 and 1940, Miss B. G. Gledhill, R. N. used Anna for a similar purpose in teaching student nurses. Anna was always willing to cooperate and to give freely of her time.

During these years, we too were learning, by microscopic and bacteriological studies of her liver and duct biles, that her relapses were definitely related to too long drainage intervals. Because of this the catarrh, the inflammation, the residual infection resident in her liver and ducts, alone or conjointly, served to throw crystals out of solution and pile them up to form minute gall stone sand and eventually larger calculi. Unless we could keep the frequency of drainages properly spaced to prevent such crystalline accumulation, we learned that Anna would relapse in'o jaundice, with pain, chills, sweats and leucocytosis. The relapse would persist until we had regained

control of the situation by energetic drainage. This, we found, would gradually remove much crystalline material, inflammatory debris, mucus and bacteria.

Early in 1925 Anna asked that she be allowed to report at the Clinic only when she felt in need of treatment. As a result, a review of the records shows that between 1925 and 1932, inclusive, she reported only 13 times for prophylactic drainage*. So on the whole, it might be fairly stated that, over a period of 12 years (1920-1932), Anna had, under the circumstances, enjoyed pretty good health. She had been able to bear, rear, and take care of her children, to carry on her domestic duties, and all of this under extremely poor economic and hygienic conditions.

On August 29, 1932, Anna passed, with flying colors, a group of liver function tests†. This, again indicates the great margin of reserve that a sick liver possesses, its remarkable capacity to recover, if given a proper chance.

Such joint good fortune, however, had lulled us to sleep. We were not sufficiently watchful of important details, especially checking, periodically, the *microscopy* of Anna's bile. As a result, a relapse occurred in June, 1933, and a second one in January, 1936. Both of these, I now believe, might have been prevented if we had been more alert to recognize the danger signal in an adverse microscopy.

So, Anna voluntarily came to the Clinic in 1933, complaining of upper right quadrant pain and discomfort. This increased to paroxysmal pain, nausea, vomiting, fever and the onset of jaundice. After so many years maintenance of Anna's good health, it was something of a shock to realize that our somnolence had made us forget to practice what we had been preaching so vigorously, namely the importance of frequent microscopic and bacteriological rechecks of a patient's bile in order to safe-guard him against pre- or post-operative relapse. In the latter case, to guard against the reformation of extra-hepatic duct stones.

Merely removing a gall bladder containing a stone or stones, and then disregarding all else, by no means implies that the patient's disease or its cause has been removed. That was a surgical fallacy that too long misled us. *Whatever formed the first stone, if allowed to exist will almost inevitably cause additional stones to reform.*

One method of approaching the prevention of advanced gall stone disease has been briefly suggested in this author's *Atlas on Biliary Drainage Microscopy*‡.

On microscopic examination of a patient's bile, if one finds great, or increasing numbers of crystals of calcium, of cholesterol, of pigment, and especially a combination of cholesterol and calcium bilirubinate crystals, this finding becomes pathognomonic of formed or forming gall stones. If one waits for such stones or gall sand to become demonstrable to X-ray, it is usually too late for successful non-surgical treatment.

I once heard a good friend of mine, a distinguished surgeon, relate, with admirable surgical restraint,

*Six of these were given between August 31 and October 26, 1925. None in 1926. One in 1927 on February 14th. Three in 1928 all in October. None in 1929, 1930 or 1931. Three in 1932 on May 23rd, September 12th and October 17th.

†The direct and indirect van den Bergh response was negative. The Icterus Index registered 3.8 units. Quantitative serum bilirubin was 0.38 mg. The bromsulphthalein dye test showed excellent liver clearance, 15% being retained at 5 minutes, 5% at 30 minutes and none at 60 minutes.

‡In 1935 one hundred copies of this micro-photographic Atlas were privately assembled. All have been sold or given to various libraries. No additional copies will be made.

from the platform of an important medical meeting, how he had removed a stone-containing gall bladder from a certain lady, and how the lady had returned annually to his clinic for removal of a common duct stone. It is a pity that the lady, or the surgeon, or his clinic had neglected to make use of duodenal tube biliary drainage at an earlier stage when it could effectively function, that is *before* the gall sand had grown to a calculus requiring surgery.

Such stones do not grow overnight. They are gradually formed by the accretion of crystals thrown out of solution in the bile, steadily or in showers. They pack together and are deposited in the numerous crevices in the rugae of the gall bladder, or in the minute canaliculi or pockets lining the mucosa of the intra- and extra-hepatic ducts. In the presence of biliary stasis, or poor biliary drainage, these crystals grow into gall sand or larger gall stone, and more rapidly will do so in the presence of infection or catarrh. If they are recognized in the growth stage of minute calculi or gall sand, occasionally even larger size stones, many such a patient can be relieved of these unwelcome accretions by duodenal tube biliary drainage, and can thus escape the pain and trauma of undergoing operation. This and other things we have learned from the case history we are describing, and many other similar ones.

Returning, now, to the chronicle of Anna, a true record of her case will show now her life was punctuated by a series of relapses with jaundice. Some were due to recurring duct sand and small calculi, some due to varying degrees of hepatocholangitis, some due to combinations of both agencies. The clinical picture often resembled Charcot's fever.

In the opinion of Drs Gibbon, Despard, and others, further surgery was inadvisable. Her treatment therefore, during these relapses, consisted of biliary drainage, attempts at disinfection of her biliary system, the use of vaccines, saline and glucose by vein and bowel, a high COH, low fat diet, general medical care, the use of decholin, decholin-sodium and in 1936 a blood transfusion. In the opinion of those doctors who took part in or who watched Anna's treatment her recoveries without recourse to further surgery were attributed chiefly to biliary drainage by duodenal tube. If persisted in, this opened her clogged up intra and extrahepatic ducts and gradually drained them of inflammatory debris and crystalline deposits, and thus permitted her liver cells to function under a lesser load.

The chronology of these relapses, their relative severity, the intervening periods and duration of good health, the prophylactic drainages, our error in allowing too long intervals between drainages, thus encouraging relapse because of gall sand or small stones, will be indicated by the following review.

Whereas Anna had had only 13 prophylactic drainages between 1925 and 1932 and had remained remarkably well, a moderately severe relapse occurred in June, 1933 which required 29 drainages between June 14 and August 30, before she was again clinically well. This was followed by 14 prophylactic treatments ending January 22, 1934.

Anna then entered her 6th and last pregnancy in February, 1934. This was more than her damaged

liver could withstand, and she suffered a more severe relapse, with jaundice. It was not clear from a group of liver tests how this might best be classified.*

No further gall tract surgery could be contemplated. A therapeutic abortion was declined. Therefore, an elective Caesarian section plus a sterilization technique, was decided upon in consultation with Prof P. Brooke Bland. This was scheduled for some time in September. At this time I hoped to get a look at Anna's liver.

Meanwhile she was again brought safely through this relapse by biliary drainage, allowing her to go to term. She was given 53 drainages between February 5 and August 27. By this time she had weathered the toxemia of pregnancy despite her damaged liver. On September 11 all brom dye was removed at 30 minutes, a five minute extraction was not made. The van den Bergh yielded a slightly positive indirect reaction. Quantitative serum bilirubin was 0.35 mg. Her bile microscopy was again normal.

Anna was delivered of a healthy baby girl by Caesarian section on September 27, 1934. A Bland sterilization technique was completed by implanting and burying the Fallopian tubes into the body of the uterus†.

At my request, the incision was enlarged upwards so that I might view the liver. *Omental pyloroduodenal and intestinal adhesions were so dense that no portion of the liver could be seen. Even the superior surface was covered by a coating like the icing on a cake.* No biopsy could be made without danger to the patient. All of the operating staff agreed that it was fortunate for Anna that biliary drainage, via the duodenal tube, had thus far successfully kept her from further biliary tract surgery.

After getting over this relapse so happily we lapsed again into error in not promptly recalling Anna to the out patient clinic. Anna's excuse was that she felt well, and was too busy nursing and caring for her new infant. Our records show that only two drainages were given her between August 27, 1934, and January 5, 1936. These were on June 12 and October 4, 1935. On the latter date, her liver and duct bile was turbid and microscopically was loaded with the tell-tale cholesterol and calcium bilirubinate crystals.

Whichever Staff doctor was responsible for not immediately ordering Anna back to a frequent drainage schedule is not now of great importance. The important point to remember, however, is that if such action had been taken she might not have suffered her last and most severe relapse in January, 1936. In all probability this could have been prevented. The accumulating gall sand and minute calculi could have been drained out before the clinical picture of obstructive jaundice had appeared.

So, Anna again voluntarily presented herself on January 15, 1936. She was in U R Q pain and mildly jaundiced. Her liver bile was pathological, a dark greenish yellow turbid, too thick, of a greasy con-

*On February 26, 1934 the van den Bergh gave a direct biphasic reaction, indirect plus one. Icterus index 8 units. Quantitative serum bilirubin 0.7 mg. Urobilinogen 1.160. But. 48%, of brom. dye was retained at 5 minutes, 27% at 30 minutes, 23% at 60 minutes. The sedimentation rate was 33.5. On May 11 when 4 months pregnant her jaundice had deepened her urine was deep reddish amber. The van den Bergh test now yielded a plus 4 direct indirect plus 4. Yet the Icterus Index registered only 12.1 units. Quantitative serum bilirubin was 1.5 mg. and urobilinogen was positive in a dilution of 1-320. †Family on relief husband on W.P.A.

sistenev, and of diminished quantity. Microscopically, crystals of calcium bilirubinate were found in abundance, occasional cholesterol and pigment crystals, some pus cells, bacteria both freely distributed and colonized, increased mucus a moderate increase in bile stained oval or cuboidal duodenal cells, and short and medium tall columnar cells from the extrahepatic ducts.

During the next three weeks Anna was given 8 drainages in the Clinic. But it soon became evident that this relapse required hospital care. Anna, again refused to return to the Jefferson Hospital wards. In my opinion this was entirely because of painful recollections of having spent so many months there in her youth. My friend colleague, and former pupil, Dr. Harry A. Bockus, now Professor of Gastro-Enterology in the Graduate School of the University of Pennsylvania, came to my rescue. Anna was admitted to his service on February 10, 1936.

At Dr. Bockus' request she carried the following letter from me to Dr. Parks, of his Intern Staff: "This will introduce Miss Anna Ingber Penn with whose case Dr. Bockus is familiar. He has suggested that I make an outline regarding her treatment and laboratory studies."

Immediate Treatment

1. A daily, or every second day, biliary drainage in the attempt to gradually remove from the intra- and extra-hepatic ducts accumulations of gall sand, chiefly calcium bilirubinate, associated with catarrh and low grade inflammation, and possible infection. Her gall bladder has been removed. Therefore, lessened amounts of magnesium sulfate will be required. Hot normal salt solution will be better.

2. Intravenous glucose, 20 grams daily for a few days.

3. Cleansing enema, followed by proctoclysis of glucose and soda bicarbonate.

4. Some form of mild alkaline therapy.

5. Decholin tablets, one tid po and decholin-sodium, 10 cc of a 20% solution by vein, every third or fourth day, if patient is not too jaundiced.

6. High carbohydrate, relatively low fat diet.

7. Heat to liver region, either by hot moist abdominal compresses, or by electric pad, but not by both.

Laboratory Studies

Routine blood counts, and blood chemistry, urinalyses, stool studies, liver function tests, routine microscopy and cultures of bile.

Thanking you for helping us out at this immediate time with the management of this patient, I am, very truly yours, B. B. V. L."

I am very grateful to Dr. Bockus for taking over supervision at this particular time. During my visits to Anna at The Graduate Hospital, and now seven years later, as I prepare this report, it was a joy to see the good team work on the part of Dr. Bockus and his well trained staff. It indicates what medical drainage can accomplish when carried out by experts. That the reader may see an example of a properly trained gastro-intestinal department, functioning smoothly in a first class hospital, I am setting down

*Over a three hour drainage period in normal subjects we have usually recovered an average of 200 cc. of liver bile. (See page 76). In sick subjects when the liver is subfunctioning, the amount of liver bile will often drop below 100 cc. to even 50 cc. This in non-jaundiced patients.

here an abstract of pertinent portions of Anna's history, her physical examination, her treatment, and particularly the laboratory and technical reports.

THE GRADUATE HOSPITAL OF PHILADELPHIA

Anna Ingber Penn (Miss) Age 36. Born in Austria. Case 121821. Admitted February 10, 1936 — Discharged March 25, 1936.

Service of Dr. Harry A. Bockus.

Referred by Dr. B. B. Vincent Lyon.

Diagnosis: Obstructive Biliary Cirrhosis, with complication of common duct stone.

Summary of Treatment: Biliary Drainages, high COH diet, glucose with insulin, intravenous decholin-sodium.

Chief Complaint: Jaundice and pruritis.

Present Illness: Since her last pregnancy in 1934, patient has done well until five weeks ago. She then developed sudden pain in the U.R.Q., referred to the back. Nausea, but no vomiting. After more severe pain, lasting 24 hours, she became jaundiced. She reported back to Dr. Lyon's clinic on January 15. She was given biliary drainages and glucose injections 2 or 3 times a week, until she was transferred here on February 10. She still has pain of a dull character in the U.R.Q. Jaundice of a mild degree has persisted. At onset of attack she had chills and fever. 20 lbs weight loss in 2 months.

Physical Examination: Essentially negative, except as follows:

1. Moderately jaundiced skin and sclerae. Skin scratched because of pruritis.

2. Poor oral hygiene. Several devitalized teeth.

3. Abdomen: Thick panniculus. Liver enlarged to 2 fb below costal margin, hard, uniform consistency. Edge very tender. Spleen is palpable to 1 inch below costal margin, in anterior axillary line, hard and firm. Upper right rectus 5 inch scar, lower midline 4 inch scar. Tenderness over U.R.Q.

4. Finger nails are scarred and brittle.

SUMMARY OF HISTORY AND CLINICAL FINDINGS

1. Worms—long, round, white—as a child. Vomited them.

2. Empyema of gall bladder at age 12. Fever, chills, severe pain, jaundice, no nausea or vomiting. Cholecystostomy.

3. Over next 4 years had a cholecystectomy and choledochostomy, with removal of stones, followed by a biliary fistulectomy, followed by a second choledochostomy and removal of common duct stones. Each time patient had obstructive jaundice.

4. Age 17 to 20. Frequent biliary drainages. Relatively symptom free.

5. Age 20 to 30. Four pregnancies, all precipitate deliveries. Over this period was symptom free with only occasional B.D.

6. After 6th pregnancy, two years ago, she had recurrence of U.R.Q. pain with jaundice, nausea and vomiting. 8 months Caesarian section and sterilization.

7. Five weeks ago had severe U.R.Q. pain. Jaundice developed after 24 hours. Nausea, vomiting. Clay stools, dark urine, pruritis.

8. Admitted here on 2-10-36. Anemic. Given infusions of saline and glucose frequently. On 2-15 temperature rose to 102. Blood transfusion (350 cc.) was given on 2-19. Biliary drainage twice weekly.

Intravenous decholin-sodium, after de jaundicing
High COH diet

9 Discharged on March 25, 1936 Improved Liver
damaged

Laboratory Observations

BILIARY DRAINAGES			
Date	Total Liver and Duct Bile	No. of Stim	Microscopy
2 11 36	50 cc	2	Flocc plus 2 Brick red Greenish yellow and orange calcium bilirubin plus 4
2 11	30 cc	3	Mucus plugs. Bile stained pus and biliary tract cells. GY calcium bilirubin crystals
2 22	85 cc.	3	Mucus plugs Granular debris. Flocc plus 2 Calcium bilirubin crystal ls.
2 25	65 cc	2	B.s. columnar and pus cell Bact. plus 2 Tyrosin cholesterol, calc bilirubin crystals.
3 7	75 cc	2	Mucus bact. wbc bile salts flocc plus 1 occasional cholesterol crystal
3 10	105 cc	3	Mucus bact wbc columnar cells b.s. flocc. plus 1 calc bilirubinate
3 14	77 cc	2	No microscopy
3-17	100 cc.	3	Mucus bact. wbc epith cells b.s. occas. flocc occas calc bilirubin crystal

LIVER FUNCTION				
Date	Quantitative Serum Bilirubin	6.0 mg	Brom dye	40%
2 11		2.1		Urobilin 1 to 10
2 22		3.8		
2 25		4.0		Urobilin 1 to 20
3 7		2.0		Urobilin 1 to 10
3 10		1.5		Urobilin 1 to 50
3 14		1.4		
3 17		0.5		Urobilin 1 to 10

SERUM PROTEIN				
Total	2 11	2 17	3 24	2 11
Protein	6.19%	5.74%	8.54%	
Albumin	3.625	3.534	4.551	Fibrinogen 1.438%
Globulin	3.184	3.247	4.13	
Ratio	1.011	1.05	1.011	

GALACTOSE TOLERANCE			GLUCOSE TOLERANCE		
Date			Date		
2 12 No. 1	2.0%		2 13		
	40 cc urine	0.500 gm	12 cc	0.096 gm	
No. 2	0.6%		16 cc		
	51 cc urine	0.406 (7)	8 cc	0.128 gm	
No. 3	0.4%		0.26%		
	148 cc urine	0.502	7 cc	0.175 gm	
No. 4	0.3%		0.12%		
	217 cc urine	0.651	2 cc	0.0324 gm	
No. 5	0.2%		0.04%		
	272 cc urine	0.544	97 cc	0.0329 gm	

2 20 Sedimentation Index—74 mm

BLOOD EXAMINATIONS				
Date	2-11	2 12	2 13	2 17
R.B.C.	3 960 000	3 940 000		4 200 000
Hb	55% 13 gm			60% 12 gm
W.B.C.	8800		8300	4900
Pmn	60% 5284		56%	59% 2891
Eosin	3% 264		1%	1% 49
Lymph	35% 3168		43%	
Basoph	1% 88		No shift to left	40% 1960
			Coag time 4 1/2 minutes	Landsteiner O
			Clot retraction normal	
				Fragility Hemol begun 0.42 Complete 0.25

URINALYSES				
Date	Color	Sp Grav	Albumin	Sugar
2-11	Dark amber	1.022	ft tr	0
3-3	Orange	1.012	0	0
3-5	Amber	1.025	0	0
3-23	Yellow	1.020	0	0

FECES				
Date	Color	Fat	Acid	Muscle
2 20	Or Bl neg	neut. 1	Acid 2	Unstriated 3
3 6	Or Bl. neg	neut. 0	Acid trace	Striated 2
3 23	Or. Bl. neg.	neut. 0	Acid trace	Striated 1

After Anna was discharged from the Graduate Hospital on March 25 1936, she returned to the clinic at Jefferson. She was given 22 biliary drainages between March 27 and December 28, 1936. She was given 5 drainages in 1937. Four in 1938 and four in 1939. Three in 1940. Two in 1941. And two in 1942 up to June. In my opinion, this is too few. It may be due, partly, to the fact that I have been on 'sick leave' from the Clinic since early in 1940. This adds up to a total of 161 drainages given Anna in the Stomach Clinic of Jefferson Hospital, exclusive of 8 which she received at the Graduate Hospital, over a period of 17 years.

It is more important, however to emphasize that, despite the seriousness of some of these relapses an occasional biliary drainage has served to give Anna an additional six year period of excellent health.

In order to prepare this 25 year review of her case, I wrote to Drs Henry J Bartle and C W Wirts, Jr, of the Clinic Staff, requesting that they admit Anna to the women's medical ward under the service of Prof Hobart A Reimann in May, 1942. This represented the 25th anniversary of her becoming the first person to receive, what was then called, "Non-surgical Drainage of the Gall Tract."

I am greatly indebted to Dr Bartle and to Dr Wirts for assembling, reviewing, and sending on to me the voluminous material necessary for preparation of this report.

The purpose of this final clinical and laboratory recheck was to appraise, as accurately as we could, the degree of liver damage and general health deterioration that Anna had sustained after 30 years of biliary illnesses, involving much surgery, and after 25 years of medical management chiefly by duodenal tube biliary drainage.

Anna was therefore readmitted, for the twelfth time to Jefferson. The following is a transcript of this admission under the House Resident service of Dr J A Hindle.

THE JEFFERSON HOSPITAL OF PHILADELPHIA

Mrs Anna Ingber Penn Age 42 939 N 6 St Philadelphia, Pa

Admitted to service of Dr H A. Reimann on 5-3-42
From Stomach Clinic. Discharged 5-8-42

Diagnosis Under Observation

Final Impression We find this patient in a remarkably satisfactory state of health, under all circumstances, and especially so as regards her biliary system.

For previous history please consult former admissions, beginning in 1912.

Present Illness Patient states that she enters the hospital at the request of the Stomach Clinic, of the Curtis Clinic, for a routine check up, and particularly to appraise her biliary system. During the past six years she has been well with no attacks of her former trouble. There is still a dull ache in the URQ but she has suffered no severe pain or colic, nor has she had jaundice, fever, nausea, or vomiting. During this time she has reported at the Clinic at stated intervals, usually every six weeks, for clinical review, and three

or four times a year for biliary drainage. She has not been on any rigid diet.

SYSTEM REVIEW

Head Occasional headache, associated with dizziness and faintness. Occasional hot flashes. Increased nervousness.

Ears Discharge from both ears. No deafness, tinnitus, or pain. Only slight vertigo. Refer to Ear Clinic.

Teeth and Gums Requires dental care. Poor hygiene. Refer to Dental Clinic.

Chest No symptoms.

Abdominal and GI No change in appetite. Occasional belching, acid eructation, and abdominal distension. Constant dull URQ ache. No constipation, diarrhea, or melena. Otherwise negative.

Genito-urinary Negative.

Menstrual Every 28 days, 3-4 days, 5-6 pads, no intermenstrual spotting.

Physical Examination Short, sturdy, swarthy, well developed and nourished female, looking older than her stated age. Considerable arcus senilis. She lies flat in bed. No pallor, or edema, or jaundice.

Eyes Normal reflexes. Arcus plus.

Ears Mucopurulent discharge, obscuring drums and usual landmarks. **Nose, throat and neck** are negative. **Tongue** slightly coated.

Chest Moderate degree of emphysema. Otherwise negative.

Heart No evidence of pathology, or disturbed function.

Abdomen Two well healed scars, URQ and pelvic. No herniae. Tender in URQ. Liver edge palpable 1 inch below costal margin, and edge feels firm, rounded, and is quite tender. Spleen doubtfully palpable*. Tuning fork test (Lyon) was strongly positive for adhesions between pyloro-duodenal segment and liver, probably not involving colon.

Extremities Dermatitis of hands. Deep reflexes are negative.

Impressions (Dr Hindle) 1 Biliary pathology, associated with URQ adhesions. 2 Impending menopause syndrome. 3 Emphysema mild. 4 Chronic otitis media.

LABORATORY REPORTS

Blood

1 RBC 4,200 M, Hb 84%, WBC 7500. Neutrophils 78%, (young forms 10), eosinophils 2%, lymphocytes 20%.

2 Wassermann and Kahn are negative. Prothrombin, 100% average normal.

3 Urea nitrogen, 9.43 mg, cholesterol, 272 mg, phosphate, 77 mg, phosphorus, 2.7 mg, protein, 6.6 mg.

4 Albumin, 3.35 Globulin, 3.25 Ratio, 1.09.

Liver Function All biom dye removed. Serum bilirubin, 0.7 mg van den Bergh, negative direct. Hippuric acid 24 gms excreted as benzoic acid in 24 hours. Bile pigment in urine, negative on 3 examinations. Urobilinogen, positive in dilutions of 1:20, 1:50 and 1:50.

Feces Contain normal amount of bile pigment.

Urinalyses Normal.

Urea Clearance 102% of average normal.

*To Dr Hindle the spleen appeared palpable 8 finger breadths below left costal margin but could not be felt by either Drs Bartle or Lyon.

Biliary Drainage Microscopy done by Dr Bartle and Dr Lyon.

"A" bile 30 cc, light yellow, turbid, slimy, amorphous sediment plus 2 Micos, Amorphous debris. Bile stained mucus with slight oleaginous degeneration. No WBC, epith cells, or Xtals. OccBl 0.

"B" bile None.

"C" bile 105 cc, darker amber than normal, slightly turbid, slimy sediment, plus 1 Micos. Essentially normal. Some bile stained mucus with bile salts, occasional duodenal cell, very occasional cholesterol crystal. No calcium bilirubinate. No columnar epithelial cells. **Impression** Normal, except for mild catarrh of extrahepatic ducts and moderately sluggish liver excretion.

X-ray of Mastoids Old bilateral sclerosing mastoiditis.

Temperature 98 **Pulse** 80 **Respiration** 20

Blood pressure $\frac{118}{60-68}$ $\frac{122}{60-68}$

COMMENT

Has the amount of liver bile recovered by duodenobiliary drainage either diagnostic or prognostic significance? In my opinion, yes. This opinion is based upon the following observations.

(1) Over a three hour drainage period in normal 'controls,' that is in patients who are not sick, or in most patients who present at a gastro-intestinal clinic, but not complaining of biliary tract symptoms, I have long noted that the amount of total bile, or of bile mixtures, recovered will be somewhere between 250 and 300 cc. Of this amount, 30 to 75 cc may be gall bladder bile. The remainder will be liver and duct bile, or bile mixtures. This is gastro-duodeno-pancreatic juices mixed with bile.

Therefore, I have taken 200 cc of liver bile as the figure most nearly representing the average amount that can be recovered by duodenal tube from the normal liver, over a three hour drainage period, and using three stimulations. This calculation is based upon several thousand drainages.

(2) In patients obstructively jaundiced because of 'ball valve' stone or of gall sand, or because of catarrhal jaundice after the mucus plug or plugs have been extracted, the amount of liver bile recovered may greatly exceed this figure. This is explainable because the bile already manufactured (secreted) is held back from excretion, dammed up by the obstruction. The liver is found enlarged, swollen and tender, partly because of bile retention. In such cases it is just as important to slowly decompress the liver by duodenal tube drainage, as the surgeons have found necessary when draining a liver by choledochostomy, or by cholecystostomy with patent cystic duct.

(3) On the other hand, one will encounter patients with varying degrees and perhaps types of hepatitis or hepato-cholangitis, and, in some instances cirrhosis. In my experience, such livers seem to lose their ability to manufacture, secrete and excrete bile. Using the same technique in these patients the amount of liver bile recovered, instead of being the usual 200 cc, will drop below 100, or even below 50 cc, as has been noted in an occasional case of subacute necrosis.

The reader will see that this occurred in Anna's case, if he will study the amount of bile recovered at the Graduate Hospital, (see page 74), while she was

in serious relapse. Her first four drainages yielded an average of 575 cc of liver and duct bile. As she improved, her second four drainages averaged 888 cc. She was discharged on March 25 and told to report at the Jefferson Hospital Stomach Clinic. A review of these records shows that her next four drainages, given on 3-27, 3-30, 4-15 and 4-20 averaged 195 cc. The following four, on 4-27, 5-4, 5-11 and 5-18, dropped back to an average of 155 cc. This latter figure roughly represents the amount that Ann's damaged liver can secrete, when averaged over her 169 biliary drainages. It is not improbable that this may be because a varying number of her liver cells are not functioning as a result of temporary suppression of cell function because of hepatitis, or of cell destruction because of cirrhosis.

THE PROBLEM OF GALL STONE DISEASE

In solving the problem of gall stone disease surgery is important, but not all important. The abdominal surgeon, experienced in this field of work, will join hands heartily, with the research physician in not appraising the gall stone problem merely in terms of manual dexterity, surgical technique and judgment. He will not diminish their importance, nor will he overemphasize them. But he will steadily try to improve his technique and his judgment, and thereby his results. He will also, remember the relative clumsiness and heavy handedness of his own apprenticeship days. He, better than any internist, knows the menace of clumsy and inexperienced surgery. He knows that a clumsy or inexperienced surgeon can remove an uncomplicated, stone-containing gall bladder. But he also knows that such a surgeon may become lost in a maze of adhesions, that he may miss an impacted cystic duct stone, or fail to discover small stones pocketed in the common duct. He knows that in such an event the patient will gain little from the operation, and may, after each succeeding operation, suffer additional traumatic effects. He knows that such surgery retards the progress of surgery.

Many a clinician, including this writer, lacking surgical hands, greatly envies the skillful and conscientious surgeon and has a profound respect for his accomplishments. But he equally deplores and is saddened by the disastrous results of the clumsy or inexperienced surgeon, results which occasionally, and unhappily occur despite the hands of a master surgeon.

As I have indicated at an earlier point, it is my opinion that gall stones are gradually formed by the packing together of myriads of minute crystals which have been thrown out of solution in the bile. It takes varying rates of time to grow a gall stone of size *in vivo*. Is it days, weeks, months or longer? I know of no one who knows exactly how long. This, no doubt, will vary with the rate and quantity with which crystals are thrown out of solution, the alterations in metabolic processes and chemical variations of the individual patient, the sluggishness of bile flow, the dilatation of bile ducts, both within and without the liver, the degree of inflammatory edema and debris, the amount of catarrh, the presence of and particularly, the virulence of infection. Some, and at times all, of these factors will be active in an individual case. Therefore, the time factor of gall stone growth will always remain a variable.

In previous articles, I have emphasized the need of prevention of gall stone disease and I have indicated

some avenue of approaching the problem successfully. The ultimate objective, basic to its control or prevention is to discover some process or method of dissolving gall stones or gall sand *in vivo*, without damage to their host. This will, one day be accomplished. But until it is accomplished, the thoughtful surgeon will agree that the best 'ounce of prevention' is to properly utilize the inherent value of biliary drainage microscopy, and biliary drainage therapy by duodenal tube in the incipient and controllable stages of the disease. *It would help very greatly if every surgical clinic would add this technique to their skilled service and use it at the proper time when it will benefit the patient.*

THE ROLE OF BILIARY DRAINAGE MICROSCOPY

As years have passed I am more than ever convinced that by studying the microscopy of a patient's bile at regular intervals, as in urinalysis we can detect several of the early stages of gall bladder disease. One of these is an early stage of gall stone disease, when gall stones are in the formative stage, that is in the 'excess crystals or minute gall sand' stage. These crystals or gall sand can then be successfully removed by duodenal tube drainage in a considerable number of patients. If this controllable stage of the disease is neglected and allowed to remain unrecognized, gall sand will increase to gall stone and the patient will find himself facing a major operation.

By microscopy we can also detect the presence of gall bladder inflammation, of infection, of catarrh, and of parasitical infestation more accurately, in the early stages, than by any other method.

THE IMPORTANCE OF GOOD BILIARY DRAINAGE TECHNIQUE

It is not merely a matter of 'routine' examination of a patient's bile, microscopically, chemically, and bacteriologically. To get the best results for the patient, the technique which I have suggested and modified from time to time (5), is laborious and tedious to a degree.

It embraces the correct method of duodenal intubation, the best solutions to favor the recovery of all biles, the importance of a three hour drainage using three stimulations, how to select, by finger controlled pipette, the likeliest floccules or particles of sediment, to avoid making thick cover slip preparations, what to look for, and the various diagnostic implications (6) using at least two cover slips for each specimen of bile. And, it is important, above all, that we do the microscopic study *immediately*, and that we do not set the bile aside, on laboratory table or in the icebox, for later examination. If we make this mistake, much of the microscopic evidence will have disappeared or will have altered beyond recognition. In addition, qualitative and quantitative cultures of both liver and gall bladder bile should be made, and likewise suitable studies of their chemical and physical properties.

Trying to short-cut or to by-pass any portion of this technique merely serves to limit or to defeat diagnostic accuracy. And the patient suffers thereby.

SHOULD EVERY GALL STONE CASE BECOME A SURGICAL 'JUST'?

Generally speaking, gall stone disease, at present, is a surgical disease. There is no method other than

skillful surgeon that will yield such safe and satisfactory results. There are few diseases, the surgical correction of which is so gratifying to both patient and doctor. The operation, if a cholecystectomy, usually brings brilliant relief from the gall stone colics, from the dull, nagging ache under the right ribs, and in the shoulder girdle and upper back, often due to adhesions, from the jaundice and itching, from the awful nausea and vomiting, from the cardialgia, the heart burn and belching.

When the surgeon is truly skillful and his surgical judgment is good the results are excellent, possibly as high as 85 per cent. The mortality rate in recent years has, likewise, been greatly reduced.

Yes, late gall stone disease is best corrected by surgery. But there are certain exceptions which, in my opinion, should be subtracted from the obligatory or 'must' group. We must learn to differentiate, perhaps, along the following lines.

First. Some gall stones develop as a result of cholecystitis. Such gall bladders should be removed unless there are obvious contraindications, such as cardio-vascular-renal disease in the aged or in the feeble.

Second. Other gall stones may result because of abnormal variations in metabolism or in body chemistry, and not because of disease of the gall bladder itself. For instance, we have the metabolic, pure cholesterol stone. This is often a solitary stone, and is frequently discovered during routine gastro-intestinal X-ray study. Another variety is the 'silent or quiescent' gall stone or stones, usually of a mixed chemistry. Once again, these are often discovered by the roentgenologist and not by the clinician chiefly because the patient has suffered neither colics nor indigestion of any type.

In both of these instances, before hastily deciding upon surgery, it is important to cross-check by biliary drainage microscopy, one or more times. This is in the interest of the patient. If no excess of crystals is found in either gall bladder or liver bile we may be justified in concluding that the stone forming phase is no longer operating. We may then put this patient, temporarily at least, in the 'watchful waiting' group. But it is good judgment to recheck the bile microscopy at least twice a year, and to also re-lay the patient to see if the stone has grown any larger. If during the interval, colics or gall bladder type indigestion should occur, then operation should be advised without delay. It is probable that such tactics would not increase the patient's surgical risk.

THE PROBLEM OF THE STONELESS GALL BLADDER PATIENT

The stoneless gall bladder patient requires special consideration. It has been my experience, and most surgeons agree, that less satisfactory surgical results have occurred in this group. Too many such patients have developed post-operative morbidities despite clean, skillful and decisive surgery.

We might improve this situation if we made it a rule to cross-check two tests before deciding that surgery is the wisest method of treatment. For instance, suppose such a gall bladder, when studied by the Graham-Cole test, shows good, or fairly good, visualization, concentration and emptying response. Likewise, to biliary drainage study we also find that this gall bladder possesses good evacuating power, and

that the cultures have remained sterile. Then we might justifiably put this patient in the 'watchful waiting' group, and temporarily treat him by a strict and comprehensive medical regimen. *Our former mistake was that if we did not operate upon this patient we did so little else.* This medical regimen I have called the "Three D Plan," meaning diet, drugs and drainage (7). In my experience it has restored many patients in this group to satisfactory health. If it fails, we can always fall back upon surgery. Such reasonable delay will not increase surgical risk. The experienced and conscientious surgeon, I believe will agree that surgery should be avoided in this stoneless variety of gall bladder disease whenever possible. The progress back to gall bladder health can be quite accurately gauged by noting that the pathological type microscopy is gradually changing to normal. But it must remain so, or the patient will experience a return of gall bladder symptoms. Therefore, occasional drainages, with careful microscopic appraisal, should be done at least 3 or 4 times a year. This will help to protect such a patient against relapse.

There is also a rather large group of patients in whom the Graham test shows poor filling, little or no concentration, and sluggish emptying. Checked by biliary drainage, this gall bladder fails to empty promptly or completely, or gives an irregular drainage sequence. The bile is 'off' color, and contains numerous shaggy, greasy floccules. On microscopic examination of these floccules one will note oleaginous droplets, pools or lakes of a brilliant yellow cholesterol melting from the edges and depths of coarse and usually spindled mucus. These cases can now be identified as either cholestasis of the gall bladder, a surgical disease, or as cystic duct obstruction due to catarrh. The latter is not a surgical 'must,' merely because the Graham test yields a non-visualized gall bladder. We have learned that it will usually respond satisfactorily to duodenal tube biliary drainage (8). The more stubborn cases may require a dozen or more drainages to accomplish a good result. The proof of this is a return to a completely normal response to the Graham test, and a subsidence in the clinical symptoms. If this should not occur, then the diagnosis should be interpreted to be cholestasis, or 'strawberry gall bladder' disease, which will require cholecystectomy for its correction.

CONCLUSIONS

This 25 year report of 'just one case' has taught us several things that justify the following conclusions.

First. Intelligent and friendly cooperation between the surgical and medical divisions is imperative. We should work together for the best interests of the patient. We should avoid the rivalries that have, in the past, been responsible for losing some lives or producing some chronic gastro-intestinal invalids.

Second. The sick liver has a great 'margin of reserve.' It has a remarkable capacity for recovery, if given a proper chance.

Third. Our present functional liver tests are inadequate for the accurate appraisal of an actually damaged liver such as Anna Penn's, especially during quiescent periods. Possibly some of them could be discarded. Better ones are greatly needed.

Fourth. Chronic liver disease, such as have been referred to, have a natural tendency to pathologically progress, and to symptomatically relapse, often be-

cause of neglect. We have learned that the frequency of relapse and the progress of the disease can be reduced by appropriate and keener watchfulness, and by more complete treatment.

Fifth Duodenal tube biliary drainage of the liver possesses great potential usefulness in patients like the one reported, and particularly so when further surgery is not considered practical. This author has successfully treated a large number of cases, similar in many respects to this one. Among them are cases of hepatitis, of hepato-cholangitis, of early cirrhosis, of subacute necrosis, of liver or gall bladder typhoid carriers, of patients with hepatic-intestinal toxemia (4), a diagnosis not yet officially recognized. These patients have been restored to relatively good health by adding duodenal tube biliary drainage of their sick livers, that is *external* bile drainage, to an otherwise medical or surgical regimen. The literature now contains many similar experiences reported by others.*

Sixth Most importantly, we learned that we err less if we make the drainage schedule frequent enough rather than too far apart. Especially this has proved true in patients who were as sick as Anna Penn. This should be self evident, when we consider how relatively little pathological material can be removed from the body at a single drainage session when compared to the amount left behind and still being formed. But if drainage is persisted in, and, particularly, if the method of 'continuous drainage' (5) is adopted for a week or two, a balance is struck between the rate of manufacture of pathologic material and the rate of its removal. Thereafter, such liver and duct cells as have not been destroyed, but merely overwhelmed by the toxemia of the disease and forced into temporary dysfunction, may recover sufficiently to turn the tide in favor of the patient's recovery. One is forced to this conclusion if one will follow the favorable trend of

*See bibliography in Ref. 5 pp. 181-185

liver function tests, as the patient responds to this form of management.

Seventh We suffered the humiliation of knowing that one of our trained microscopists, by failing to report the tell-tale microscopy of recurrent gall sand and failing to increase the drainage schedule, caused this patient to suffer her most recent and entirely preventable relapse in 1936. This is a human error and therefore correctible.

Eighth We were made to realize during this quarter century that the greater value of this method still remains befogged by those who persist in referring to it as 'gall bladder drainage' instead of 'biliary tract drainage.' The latter term, obviously, means drainage of the duodenum, of the liver, of its ducts, of the gall bladder, (if it still remains and its cystic duct is patent) and it may well include drainage of the pancreas. The health of many diabetics has been improved by adding biliary drainage. Explanations for this have been various.

Ninth We learned that the judicious use of this method will not preclude surgery. Nor does it necessarily make surgery more difficult. In fact it can often be wisely used to better prepare the surgical field for safer surgery. If we exhibit its use with discrimination, and selecting cases suitable for its use, the patient cannot lose. In suitable cases, this method has succeeded in reestablishing satisfactory biliary tract drainage removing gall sand and the products of inflammation and infection from the gall bladder and the hepatic ducts. But the pendulum should not be allowed to swing too far.* However, if this method fails and a gall stone of size develops and colics ensue then there is only one course left open to the patient. Surgery, clean, skillful, decisive.

*A surgical clinic in South America insists that in gall stone cases duodenal tube biliary drainage shall be a pre-operative must and they report the recovery in the stools of numerous gall stones. We deprecate this as being meretricious, unwise and dangerous and have so advised them.

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Notes On Nutrition

In spite of the difficulty of assessing the actual diets which have been eaten by an individual or group through any method of recording, and in spite of the fact that hospital populations are not typical of the whole there seems to be evidence that many diseases are implanted on a background of dietary deficiency and that actual specific avitaminoses particularly pellagra are much more common even in northern states than has been supposed. In the U S A, most cases of dietary deficiency seem to exist in those persons who, while not in 'buoyant health' are not ill enough to seek medical attention. (*J A M A*, 118:944, 1942), (*J A M A* 119:1475, 1942).

Sulfonamide drugs and hypoprothrombinemia
Feeding sulfaguanidine to rats on a purified basal

ration caused growth retardation and hypoprothrombinemia effects were antagonized by the addition of liver extract and p-aminobenzoic acid. It is therefore suggested that liver extract and Vitamin K be used to counteract hypoprothrombinemia arising from sulfonamide therapy. (*J Biol Chem* 145:137, 1942).

There are two schools of thought respecting the uses of vitamins. One holds that many persons derive benefit from supplementing their diets with synthetic or purified vitamin mixtures, the other believes that it is irrational, nutritionally unwise and uneconomical to give vitamin pills to presumably healthy adults. The report of the Council on Pharmacy and Chemistry and the Council on Foods and Nutrition of the A M A take the attitude that multiple vitamin therapy is

valuable in the practice of medicine not only in the cure but in the prevention of multiple vitamin deficiencies. The War Production Board rules that not more than 5000 units of Vitamin A may appear in the recommended daily quantity of vitamin products (J. A. M. A., 118 618, 1942).

The superior nutritional values of milk from cows on pasture as compared with those fed winter rations probably depends to some extent upon the influence of the "grass juice" factor, but there is also noted a difference in the proportions of fatty acids in the two milks and while these differences are hard to account for on the basis of what the cow eats it may be a factor in the nutritional value of the milk (J. Soc. Chem. Ind., 60 305, 1941).

Vitamin A liver storage. It has long been known that liver storage of Vitamin A was of assistance to the animal on a diet deprived of this agent, but only recently has a technique been found for studying the disposition of Vitamin A in other tissues. The fluorescent microscope technique suggests that the true liver cells are the normal site of "stored" vitamin A in the liver while the Kupfer cells destroy the excess in times of hypervitaminosis and distribute the last remnants during severe depletion. There is no distinct parallelism between the plasma level and Vitamin A stored in the liver although a high plasma level usually was found to co-exist with a high liver storage level (J. Nutri., 23 431 1942), (Proc. Soc. Exp. Biol. Med., 49 202, 1942) (ibid., 50 266, 1942), (ibid., 49 589, 1942).

Single vitamin therapy in multiple deficiency. Suitable feeding experiments were done to test the point of whether or not the administration of a B fraction to an animal whose diet was deficient in some other fraction would cure the symptoms due to the omission. Generally speaking it was found that the administration of a single vitamin had no curative effect on deficiencies in other specific supplements or fractions, although no apparent harm was done by this kind of treatment (Am. J. Med. Sci., 204 364, 1942). The injection of thiamin chloride was found to relieve the pain of "dry socket" after the extraction of a tooth, although it is difficult to explain this relief except on the basis of a possible pharmacological action of pure thiamin, quite distinct from its role in nutrition (J. Am. Dental Ass'n., 29 1445, 1942).

Encephalograms in thiamin deficient pigeons showed marked changes in voltage and frequency which paralleled the clinical course of the disease, and a return to normal, when thiamin feeding could accomplish this (Arch. Neurol. Psychiat., 47 821, 1942).

Vitamin A Nutrition and blood levels in the dairy calf were studied by estimation of the blood plasma levels of Vitamin A. Blood concentrations of 10 micrograms of Vitamin A per 100 ml of blood plasma were needed to maintain adequate vitamin nutrition (J. Dairy Sci., 25 433, 1942).

As might be supposed, the accuracy of dietary histories, when checked against actual weighing of the food eaten, was shown to be fallacious, the error being both plus and minus, and there was not one case in which the diet history method of assaying food eaten corresponded in all details with the facts as determined by weighing. Even after weighing accuracy would be increased by analysis of the foods rather than the use of conversion tables (J. Am. Dietet. Ass'n., 18 562, 1942).

In **riboflavine deficiency** in animals dermatoses and dermatitis are outstanding results, although a form of cataract has been observed to develop, and there are atrophic changes in the testicles and thyroid, although the human sign of riboflavin deficiency has been the accepted cheilosis (J. Nat. Cancer Inst., 2 601, 1942), (J. Nutrit., 16 451, 1938), (ibid., 22 345, 1941).

Mild thiamin deficiency in man was induced by a medium degree of deprivation of thiamin through special diets and these were continued for 89 to 196 days. Definite changes in personality were noted in all subjects, consisting of irritability, depression, quarrelsomeness, tendency to suicide, forgetfulness, loss of dexterity, numbness in hands and feet, headaches, backaches, insomnia, sensitivity to noises, fatigability, constipation, nausea, vomiting, hypotension, drop in metabolic rate, occasionally a macrocytic, hypochromic anemia, all of which gradually disappeared on the administration of thiamin.

Neo-beta-carotene an isomer of Beta-carotene is present in fresh plant material to the extent of from 10 to 21 per cent of the total carotene, although the Vitamin A potency of the isomer has not been determined (J. Biol. Chem., 144 21, 1942).

Synthesis of Ascorbic Acid by the Rat. It has been generally assumed that all animals other than guinea pigs and primates are able to synthesize sufficient ascorbic acid for their ordinary needs. A study of ascorbic acid production in the rat showed that maximum amounts of this acid were excreted when the animals, on USP Vitamin A free diet, were given 30 IU of Vitamin A daily. Also, stilbestrol injections increased the rate of ascorbic acid excretion, especially in castrated females. Further study showed that no particular organ or gland is involved in the synthesis of ascorbic acid, but that this synthesis is a general metabolic function (J. Biol. Chem., 144 183, 1942), (J. Biol. Chem. 135 497, 1940).

Maternal nutrition and its effect on the offspring. Although many congenital defects and reproductive failures in all animals have been tentatively explained on various and many bases, it seems probable that dietary deficiency is a very large factor. It is shown by experiments in rats that successful lactation depends largely upon a good diet. Brewer's yeast, baker's yeast, dextrin and liver filtrate contain these lactation factors. Pig liver is an excellent source of a nutritional factor necessary for the normal pre-natal bone development of the rat, in the absence of which congenital malformations and intrauterine resorption have been noted.

Biotin and tumor metabolism. Malignant tumors vary widely in their biotin (Vitamin H) content from normal tissues, some being higher (skin experimental tumors) and some lower (rat liver carcinoma). Some transplantable tumors developed as well in the absence of biotin as in the normal animal. Certainly biotin is an important dietary essential for certain mammals. The biotin content of tumors may be the result of malignancy rather than the cause.

Diet may have an important bearing on the development of toxic reactions to the administration of **sulfanilamide**. Experimentally in rats it was found that a high protein diet protected against the ill effects of large continuous dosage with this drug, probably because such a diet increased urinary excretion. Low protein diets increase the susceptibility of rats to the

toxic effects of sulfanilamide. The question unanswered is—does the high protein diet prevent effective blood concentrations of the drug?

Specificity of hemorrhagic preventive factors Hemorrhages in chicks were caused by a Vitamin K deficient diet and the chicks were protected from the hemorrhages by the addition of a Vitamin K preparation made from alfalfa hay, although no protection was afforded by hesperidin, or ascorbic acid or Vitamin D, even in massive doses (Poultry Sci., 21 256, 1942)

Emergency nutrition researches in wartime In England it was experimentally determined that good bacon was produced in pigs which had been fed a balanced "swill." The best swill is a garbage collected in August and dried, being thus easily transported or stored. Pigs eating a diet composed of 95 per cent dried balanced swill and 5 per cent bran were leaner than average, they were classified in preferred grades by meat experts and there was no tendency toward "soft bacon" (J Agr Sci., 32 85, 1942)

Thiamin in American Diets By the use of various studies bearing on the problem, it was possible to make a thiamin extraction from what was considered the average diet used in America and the results suggested that cereals and meat each supply one-fourth of the thiamin eaten, that dairy products and vegetables supply one-fifth, and fruits about one-tenth. Pork, milk and bread appear as the principal contributors to the total American diet and if the conventional white bread were replaced by "enriched bread" in such a diet, the cereals would supply one-half the total thiamin and the total thiamin intake would be near the ideal estimated amount of 0.6 mg per 1000 calories (J Nutrition, 23 613, 1942)

Nutrition and lesions of the tongue Syphilis and tobacco are not alone responsible for leukoplakia, as diet is at least an additional factor. Oral lesions were enhanced by increased incidence by achlorhydria alone or in association with hepatic insufficiency, and with an associated low Vitamin A and riboflavin metabolism, the question arose as to whether leukoplakia and papillary atrophy might not result from a primary avitaminosis due to the impaired functions of the gastro-intestinal tract. Papillary atrophy responded in 80 per cent of cases to heavy administration of brewer's yeast but leukoplakia did not so respond (Cancer Research 2 381 1942)

Cooking of vegetables Pressure saucepans have a slight advantage with reference to Vitamin C and phosphorus retention over open kettles for cooking but the appetizing effects of the two methods were reversed (Food Research, 7 300, 1942)

B vitamins required to prevent dental defects Experimental feedings on dogs showed that the filtrate fraction of Vitamin B (pantothenic acid and other unidentified members of B-complex) and nicotinic acid are essential dietary factors for the prevention of gingival pathology and an inflammatory type of parodontosis. Osteoporosis resulted from the lack of filtrate fraction. A deficiency in nicotinic acid alone leads only to gingival disturbances without subsequent dental or osseous changes (J Periodontology 13 18, 1942)

Absorption of nutrients from whole wheat flour and bread As a result of experiments made on men and

women over a period of nine months in which the effects of eating diets the bulk of whose calories came from wheat either from white flour or the "national meal" flour, it was concluded that white flour was as good, and in some way better than whole wheat flour. This seemed especially true when the metabolic balance of minerals were studied by stool and urine analysis along with food analysis. Their conclusion ought to be taken with reserve because their diets were not planned in accordance with the well-known principle that for the study of any one ingredient, the diet should be adequate with respect to all other known factors. They did not have any control over the amount of fresh fruit consumption which definitely affects calcium balances. Most of the subjects were in negative calcium balance most of the time due to the restriction of milk. This and other considerations make it appear that the results should be accepted with reserve, as well as the English procedure of using a wheat meal of 85 per cent extraction fortified by calcium carbonate and the addition of thiamin to white flour (J Physiol, 101 44, 1942), (Lancet, 242 588 1942)

Chastek Paralysis in Foxes and Wernicke's Disease in Man Chastek paralysis is an acute dietary disease of foxes first observed on the fox ranch of J. S. Chastek, Clencoe, Minnesota. The disease is caused by including 10 per cent or more of uncooked fish in the ration of the fox and may be cured or prevented by giving adequate amounts of thiamin. The central nervous system pathological changes of Chastek paralysis closely resembles those of Wernicke's disease and the greater incidence of hemorrhage in the former may be due to species differences or to the fact that in the human disease other deficiencies are also present. But thiamin does reverse the ophthalmoplegia and helps the state of clouded consciousness in human syndrome (Am J Path., 18 79, 1942), (J Nutrition, 21 243, 1942) (Quart J Studies on Alcohol 2 73 1941)

Food to Allied Nations The Agricultural Marketing Administration (AMA) shipped nearly 600,000,000 pounds of food and other agricultural commodities to Allied Nations in July, of which grains and cereals comprised 148,000,000 lbs., meats and fish 122,400,000 lbs., dairy products and eggs 64,000,000 lbs. During the 3 months prior to August 1 we sent to the Allied Nations 7530 lbs. of ascorbic acid and 5738 lbs. of thiamin. Wild Rice is an excellent source of nicotinic acid. The WPB recently requisitioned 80 per cent of all canned salmon sardines and pilchards from the 1942 pack for military forces and Lend Lease, with release for civilian consumption if and when these other needs are met. Read *A Symposium on Respiratory Enzymes* edited by Perry Wilson, Univ. Wisc. Press, Madison, 1942 pp 281 and *The Biological Action of the Vitamins*, edited by E. A. Evans, Jr., Univ. of Chicago Press Chicago, 1942, pp 225. Address the Council on Foods and Nutrition A. M. A., 535 N. Dearborn St., Chicago and ask for *Food Charts* which show the sources of the dietary essentials. At Albany and at Rochester New York have been set up training schools in food dehydration conducted by Agricultural Research Administration and the Agric. Market Admin., which is the Lend Lease purchasing

Adenylic Acid in the Treatment of Agranulocytosis and Mucous Membrane Lesions

"Some Biochemical Aspects of Leukopenia"

By

SIMON L. RUSKIN, M.D.
NEW YORK NEW YORK

DESPITE our knowledge of Vitamin B Complex and the individual factors that are already common knowledge, there still has persisted the feeling that whole dried yeast and liver powder possessed an element of important nutritional value not yet isolated. Martin and Koop in discussing the precancerous mouth lesions of avitaminosis B described the advantages of dried granular yeast particularly in its good effect on the morale of the patient and the feeling of well being which they derive from it. They also observed after administration of dried granular yeast, a marked improvement in stomatitis and chronic erosions of the mucous membrane of the mouth and tongue. They are of the opinion that these beneficial results are due, not only to the commonly associated elements of the B Complex, but to other factors which they have not yet investigated.

It is the object of this paper to show that the element of the B Complex largely responsible for the improvement in the mucous membrane lesions as well as the general feeling of well being, increased energy, and improved morale, is to a large extent due to the adenylic nucleotide present in both yeast and liver powder. Further it is here suggested that nucleic acid representing all four nucleotides be regarded as an essential component of the B Complex.

In our study of the B Complex, it is strange that the very core of the germinal materials obtained from the vegetable embryo and from yeast or liver which is essentially the nucleic acid has been excluded from the classification of vitamins. Unfortunately, our knowledge of the physiological activity of the nucleotides comprising the nucleic acid is incomplete. However, from the data that is accumulating at present, there can be no doubt that nucleic acid and its nucleotides will take its place in the B Complex. Already one of the four nucleotides, adenylic acid, which has received the greatest amount of study is admitted. Spies et al, have shown that pellagrins in relapse are benefited by treatment with nicotinic acid and adenylic acid. Six patients with malnutrition who had intense burning of the oral mucous membranes but no diagnostic evidence of pellagra, were relieved following treatment with adenylic acid alone. Spies' work would tend to place adenylic acid in the B vitamin group.

The important relationship of nucleic acid to water metabolism runs remarkably close in its action on edema to that of thiamine chloride. The thiamine itself has the same pyrimidine structure possessed by the nucleotides of nucleic acid. I have described the relationship of nucleic acid to water metabolism in my article on "The Mechanism of Nephrosis in Sinusitis

in Children" and have shown that the reduction of edema by the ingestion of nucleic acid is in many respects similar to the improvement obtained with thiamine chloride. I have attributed this influence on the water metabolism to the fact that in the oxidation of the pyrimidine of nucleic acid the end products are urea, CO_2 and pyruvic acid. Though urea acts as a potent diuretic, the CO_2 may serve as a factor in the regulation of cerebral circulation and the pyruvic acid is further metabolized under the influence of thiamine (carboxylase). We thus have an intimate relationship between Vitamin B¹ and the nucleotides. A similar enzymatic relationship in the energy release and utilization of sugar occurs from the action of the pyridine adenylic nucleotide.

The adenylic nucleotide has been the object of very extensive physiological investigation, all of it showing an important relationship between adenylic acid and the blood vascular system. It not only causes a peripheral vaso dilatation, and increase in coronary circulation, but also has a unique effect in elevating the whole blood picture, thus hemoglobin, red cell count, and white cell count are simultaneously increased.

In my presentation of this effect to the American Chemical Society meeting in St. Louis, I advocated the general use of the adenylic nucleotide in those cases where sulfonamide drugs show a tendency to toxic influences on the blood vascular mechanism. Clinically adenylic acid as the non salt has been extensively used for several years. Ruskin and Katz in an article on the "Therapeutic Action of the Nucleotides" showed in a series of wide variety of cases a uniform elevation of the whole blood picture associated with a rapid feeling of well being and unique improvement in morale out of all proportion to the amounts used.

All of these physiological activities of nucleic acid and the nucleotides point to their vitamin character and argue for their admission into the B Complex group. This paper is however, concerned with the study of mucous membrane lesions most pronounced in those diseases characterized by leukopenia and manifested in the extreme in the clinical picture of agranulocytosis and their relation to the nucleotides. It is the further object of this paper to correlate the favorable action of whole dried yeast and liver powder on mucous membrane lesions of the mouth and tongue with adenylic nucleotide and the other nucleotides of nucleic acid. An attempt is also made to show that the wide variety of causes leading to lesions of the mucous membrane have a common underlying mechanism that involves nucleic acid and the nucleotides.

Our thinking of avitaminosis in terms of intake deficiencies must also be revised, insofar that chemical

substances produced in the body by bacteria, or ingested in the form of drugs, or physical agents to which the individual is exposed, may neutralize or block the essential action of an adequate supply of ingested vitamins. A typical example of such neutralizing relationship exists between avidin and biotin. Likewise, an overdosage of thiamine may influence the activity of riboflavin. B. coli may destroy ascorbic acid. In nucleic acid itself, the four nucleotides are balanced against each other between the purine and the pyrimidine nucleotides in precisely the fashion that avidin bears to biotin. Thus, the action of nucleic acid on the circulation is very slight whereas that of the isolated adenylic nucleotide is very profound. A study therefore of the factors that disrupt this balance is in itself a new method of approach to the study of disease.

In considering lesions of the mucous membrane one must first recognize the biochemical essentials of the healthy mucosa. The mucous membrane secretions can be viewed as an organic outer layer noncellular in character similar to the cellular cuticular layer of the skin rather than as a foreign body extruded as a waste product. It forms as such an essential component of the mucous membrane. Any factor preventing the formation of the mucous membrane secretion simultaneously disrupts the membrane and exposes it to bacterial invasion as certainly as the loss of the cuticular layer of the skin, perhaps more so. Loss of the secretions of the mucous membrane leads to dryness, redness, swelling, ulceration and eventual necrosis. In this manner there may be formed the ulcero-necrotic lesion. Long before the advance to this terminal pathologic stage, the loss of the mucous membrane secretions can be observed by simple staining methods such as painting the membrane with a solution of silver nucleinate. It will then be observed that the silver stains deeply into the tissue instead of the customary superficial coloration.

A study of this mucous membrane secretion shows it to be made up of mucin and nucleoprotein. The mucin is a relatively inert material. The nucleoprotein however is a vital component of the mucous membrane secretion and as Tichomiroff has shown, can precipitate some bacterial toxins as well as actively inhibit bacterial growth. From my studies, it appeared that the nucleic acid radical was the one most involved in this mechanism.

The fact that virus structure has been demonstrated by Stanley to be identical with nucleic acid gives us still further reason to consider nucleic acid as a possible anti-virus. The significance therefore of nucleic acid in normal mucous membrane health, leads us simultaneously to a regard for its importance in the occurrence of lesions of the mucous membrane and explains perhaps the underlying mechanism for the improvement clinically of mucous membrane lesions under Vitamin B (yeast) therapy and the occurrence of the lesions in B. Avitaminosis. Thus B. Avitaminosis doubtless also represents nucleotide deficiency.

To illustrate this point, I am citing in this report a case of agranulocytosis that was by all clinical judgment of the severe fatal type but which recovered by the simultaneous administration of yeast adenylic acid in substantial dosage in the form of iron adenyate (Ironyl-Squibb) and muscle adenylic acid in the form of liver extract. The clinical improvement started

dramatically with the administration of the iron adenyate. I am attempting, in this paper, to show the wide variety of mucous membrane lesions and the unanimity of their relationship to nucleic acid and the nucleotides. I am incorporating a somewhat detailed description of the biochemistry of nucleic acid so essential for the understanding of the nucleotides.

The chemistry and physiologic action of nucleic acid and the nucleotides is in itself large enough to merit a division of physiologic chemistry.

The present study would tend to indicate that leucopenic diseases may be put in one group as far as their reaction to adenylic acid is concerned. Also the common association of mucous membrane lesions and leucopenia is not a haphazard one but may be related to the functions of the nucleotides. The enzymatic action of adenylic acid in carbohydrate and protein metabolism is today recognized. The influence of adenylic acid on the blood vascular mechanism and its ability to elevate the whole blood picture has already been presented by Ruskin and Katz. There remains now to show the biochemical relations between adenylic acid and the ulcero-necrotic lesions of the mucous membrane in leucopenic diseases.

Broadly we have come to recognize three sources of leucopenias, infections, intoxications, and certain metabolic states. The first we have always had with us, and we are familiar with the classical leucopenia of typhoid, diphtheria, influenza, kala-azar, the protozoal infestations, Vincents and the spirocheta of syphilis, the virus diseases, small-pox and chicken-pox. These have fundamentally lesions of the mucous membrane with frequently associated skin manifestations.

The last three decades marks the introduction of chemotherapy of the synthetic chemicals from the barbiturates, pyrazalones, benzene, and now more particularly the sulfonamides. With this whole group has come another source of leucopenia. Unfortunately, while the leucopenia of infections is more or less combated by immunologic processes and tends to become self limited, no such defense exists for chemotherapeutic induced leucopenia. As a result, following a decade of barbiturates, amidopyrine and benzene preparations, fatal leucopenias appeared as a new clinical entity, and as recently as 1922 Schultz described the first case of agranulocytosis. Here too, the clinical picture was an ulcero-necrotic lesion of the mucous membranes with or without skin manifestations.

The third group of leucopenias is that of metabolic sources including avitaminosis, pregnancy and climacterium and represents the mildest of the leucopenias yet essentially periods of chemical imbalance.

In seeking a common denominator for leucopenia one is led to the reticulo endothelial system as definitely as to the thyroid in thyrotoxicosis. The next step in the study was to determine the chemical keystones of the reticulo endothelial system. Since the nuclear elements of the blood stream are supplied by that tissue, the structure and metabolism of nucleic acid appeared the logical objective. This was particularly interesting since in an earlier study of the biochemistry of mucous membrane disturbances published under the misleading title of "The Mechanism of Nephrosis in Sinusitis in Children" I arrived at the importance of nucleic acid in the treatment of mucous membrane diseases such as sinusitis and nasal allergy.

The study of nucleic acid revealed the role of the nucleotides and their importance as a therapeutic agent. It is well for us to scrutinize their chemical structure and physiologic action and their relationship to the reticulo-endothelial system.

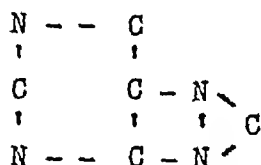
THE BIOCHEMISTRY OF NUCLEIC ACID

The nucleotides, which are four in number, are united together to form the single molecule of nucleic acid which, as its name implies, occurs chiefly in the cell nucleus and since it is a composite of a nitrogenous base, a ribose sugar related to riboflavin and phosphoric acid, it constitutes the bulk of the non-protein nitrogen in our food. As a rule, it is linked with protein radicals forming nucleoproteins that enter into the structure of mucous membrane secretions and the building stones for cell growth. That an important relationship between this non-protein nitrogen of nucleic acid and protein nitrogen exist, I pointed out in my paper dealing with nucleic acid therapy in allergic states, wherein I showed that feeding the non-protein nitrogen of nucleic acid to allergic patients definitely diminished their sensitivity to protein nitrogen. I explained this empirical finding on the basis that allergic patients are commonly those who have protracted mucous membrane infection as in sinusitis or disturbances such as colitis whereby large amounts of secretions rich in nucleoprotein have been lost. The protein radicals are easily replaced by the diet, whereas, the nucleic acid radicals are not so readily acquired. A point is reached where a deficiency in those non-protein radicals occurs and with it comes a sensitivity to protein nitrogen. I would not venture to attempt a solution of the problem of allergy on as simple a basis as this; nevertheless, the empirical fact that nucleic acid feeding is strikingly helpful, remains.

To proceed further in the consideration of the nucleotides, we find all four nucleotides have a common structure. Thus the base is united with a glucoside which in plant nucleic acid is d-ribose and in animal nucleic acid d-ribodesos, as well as to phosphoric acid. A picture of nucleic acid would be as follows:

- (— Phosphoric acid-sugar-purine (Adenylic nucleotide)
- (— Phosphoric acid-sugar-pyrimidine (Cytidilic nucleotide)
- (— Phosphoric acid-sugar-pyrimidine (Uridylic nucleotide)
- (— Phosphoric acid-sugar-purine (Guanylic nucleotide)

Let us now look closer at their chemical structure. The outer two nucleotides are purines and have the general structure



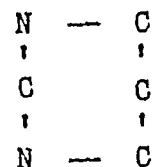
To this type of structure belong the well known stimulants and diuretics, caffeine, theobromine and

theophyllin. Adenosine, which is of this group has been shown to play a role in the stimulation of the reticulo-endothelial system, and more recently to be closely related to energy exchange in the muscle.

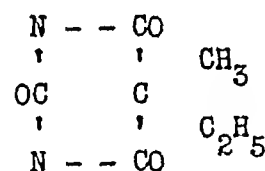
The recent report of Martin of the Warner Research Laboratory to the American Chemical Society of the stimulation of the growth of cultures of streptococci by adenine indicates the general growth stimulating properties of adenine for bacteria as well as for physiologic cell multiplication. Adenylic nucleotide, according to Martin, does not have the same effect in stimulating bacterial growth. It apparently does not influence bacterial growth. The adenylic nucleotide does, however, seem to be related to the stimulation of the reticulo-endothelial system so important in resistance to infection.

Guanine has as yet received but little successful investigation.

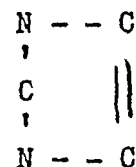
The other two nucleotides, thymine and cytosine, are again different from the purines—they are the pyrimidines and have the structure



To this group of structures belong barbituric acid and the depressants. Thus veronal would be



The change of different groups on the 5 carbon gives us a phenobarbital (luminol), amytal, etc. The still further breakdown of the pyrimidines yields hydantoin,



from which is derived the profound depressant phenyl ethyl hydantoin (nirvanol) and dilantin sodium. The final oxidation of the pyrimidines goes off into urea, CO_2 and pyruvic acid.

Thus we see that in nucleic acid we are dealing with a balanced mechanism of basic stimulants and depressants. Doven showed that the injection intravenously of the whole nucleic acid in dogs induces a narcosis and lowers greatly the coagulability of the blood.

The guanine nucleotide is probably related to CO_2 exchange, but the literature on that is almost barren.

A summary of the physiologic action of the nucleotides reveals the extent of their importance.

adenylic nucleotide to hemoglobin and erythrocyte level as well as to the leucocyte count, was demonstrated by Buell (1) points to the intimate relationship of the adenylic nucleotide in the normal functioning of the reticulo endothelial system

The role of nucleic acid in the binding of toxin has been interestingly demonstrated by the Russian investigator, Tichomiroff. Whether the toxin, be it bacterial such as in diphtheria, typhoid, or scarlet fever, which are now demonstrable, or organic, such as ricin or benzene and its derivatives, or metallic, as arsenic and mercury, the end result of the invasion of these substances is the call on the organism for neutralization of the toxin by the reticulo endothelial system. Whether this involves a drain on the nucleic acid metabolism is a question deserving of further investigation. The fact that bacterial invasions of organisms producing a definite toxin is associated with manifestations of reaction upon the part of the mucous membrane, lymphoid tissue, bone marrow and spleen, all of which are the richest sources of nucleic acid, would seem to indicate that such relationship exists.

Nucleic acid does not occur free in the blood stream, except in very small amounts, but is available through the leucocytes or mucous membrane secretions, both of which are known barriers to toxin invasion. The adenylic nucleotide, however, occurs normally in the blood stream in 22-37 mg per cent, as shown by Buell-Perkins (1). The relationship of adenylic nucleotide to the leucocyte has recently been pointed out by Lubimova (22), who showed that adenosine triphosphate, which is the adenylic nucleotide is synthesized in rabbit leucocytes during respiration.

The response of the mucous membrane to disturbance of leucocyte formation is quite typical, particularly when of chemical origin. Here as a rule one is dealing with a chronic process, although acute chemical invasion can occur as in the reported cases of dinitrophenol poisoning. Blocking of the reticulo endothelial system by chemical agents must be seriously considered as a significant factor. Clinically, the mucous membrane shows an early dry redness which may be the only indication of onset. This may be followed by the development of a dry looking edema, with subsequently a dry slough and ulceration, which in spite of a normal or elevated red blood count looks pale. It is this dryness of the mucous membrane itself that designates the failure of nucleoprotein secretion formation. It is the same dryness that has been considered of bad prognostic outlook by the older clinicians and is indicative of an overwhelming infection now correlated to failure of the reticulo endothelial system. The more favorable cases do not show this complete dryness. Edema is the direct accompaniment of the loss of nucleoprotein, and Wells (40) has shown that edematous tissues are poor in nucleic acid. In my previous work I have described the intimate relationship between nucleic acid and water metabolism. It is also common experience that excessively dried mucous membrane, not protected by its secretions, swells rapidly. It is this edema which has led repeatedly to the erroneous diagnosis of peritonsillar abscess in the early cases of agranulocytosis.

In considering nucleic acid metabolism one must recognize two possible mechanisms as occurring: one is the loss of nucleic acid, in neutralization of toxins, such as occurs in the reaction to infections like diphtheria, typhoid, scarlet fever, the other is an imbalance

in nucleic acid occurring through the upsetting of the equilibrium between the two antagonistic elements in nucleic acid, the purines and pyrimidines. Continued administration of barbiturates is equivalent to feeding pyrimidines without the balancing purines. That such an imbalance can occur is easily demonstrated by feeding phenyl ethyl hydantoin (Nivanol), a still further breakdown product of the barbiturate structure, the hydantoin. One gets promptly in addition to hypnotic effect marked leucopenia, dry redness of the mucous membrane, rash and high fever like the exanthemata.

That the chemical disturbance of this balance between the purine and pyrimidine metabolism of nucleic acid would lead to grave consequences is further borne out by the fact that some of the cases of agranulocytic angina following barbiturates respond promptly to the administration of pentose nucleotide, which is the trade name for a mixture of adenylic and guanylic acid, or to leucocytic extract or whole sedimented leucocytes.

For the guanylic acid there is still no demonstrable evidence of specific physiologic action. The adenylic acid element, however, has been intensively studied as has been described, and it alone in the form of adenine sulphate has on occasion sufficed in the treatment of agranulocytic angina as shown by Reznikoff (29). Supplying adenylic acid, which is preferable to adenine sulphate, might be considered an equalization therapy in chemical cases. If the patient survives the acute imbalance and avoids further chemical insult, the patient may recover promptly.

Nucleic acid and the nucleotides are also susceptible to the chemical action of ultra-violet rays. Pincussen and Flows (27) showed that nucleic acid exposed to the rays of a nitral lamp of 300 N K showed pronounced splitting when combined with eosin as a sensitizer or alone. Other investigation demonstrated that light radiation caused a further oxidation of the purine bases. We see, therefore, that the physical agents likewise can produce an inequality in the balance between purine and pyrimidine nucleotides with the preponderance of the latter inducing leucopenia.

We see, therefore, that in dealing with leucopenic states we are confronted with a variety of mechanisms, bacterial toxins, therapeutic toxins, chemical and physical toxins, all of which are alike able to disturb the nucleic acid metabolism producing a closely related clinical picture. The failure, however, of nucleotide therapy in some cases indicates that other unrecognized chemical mechanisms besides that of nucleic acid may disturb the normal reaction of the mucous membranes.

An experimental approach to the relationship of the nucleotides to diphtheria toxin was carried out informally by Mr. Greenwald at the Board of Health laboratory and myself. We found that animals receiving a lethal dose of diphtheria toxin and a simultaneous injection of manganese nucleotide survived, while those not receiving the nucleotide died. A similar experience occurred in a series of four severe typhoid cases seen by Dr. R. E. Lopez. It was in a family where two children and the father contracted typhoid from a newly hired cook. On my recommendation one of the children received daily for three days an ampoule containing 2 cc of a 3% solution of manganese nucleotide. The child's white blood count rose

from 2,000 to 8,000 in forty-eight hours. She was the only one of the three who survived.

In a previous joint publication with Dr. Elhu Katz we presented a series of twenty cases of moderate leucopenias of various types which were improved by the administration of iron nucleotide (Ironyl Squibb).

Thus we see that it is necessary to consider agranulocytosis by viewing the whole picture of leucopenia and the entire group of conditions manifesting depression of bone marrow function. In this connection we must group together infections, intoxications, and physiologic derangements involving the reticulo-endothelial system, and inducing among other signs a depression of the white cell count.

When we do this we enlarge our concept of mucous membrane lesions and their relation to nucleotide therapy. An added factor in the treatment of typhoid fever, diphtheria, and the gamut of leukopenic diseases thus appears on the horizon. In addition, attention is focused on the prophylactic value of nucleotide therapy in milder cases not suffering from the profound ulceronecrotic lesions of advanced leukopenic states, but rather like those cases described by Roberts and Kracke (30) showing fatigability, nervousness and insomnia, so commonly observed by them in

women over forty, and associated with moderate leukopenias. In this group of cases the uses of the ferrous salt of adenylic acid has been extensively described in a previous article by Ruskin and Katz (36), which demonstrated the elevation of the whole blood picture by the daily administration of Iron Adenylate.

The enormous contribution to therapy which the sulfonamides represents poses a critical problem not only for the early recognition of leucopenia and cessation of therapy, but also the correction of leucopenia with the possibility of a resumption of sulfonamide treatment. In the adenylic nucleotide we have the possibility of aiding in resistance to infection and simultaneously correcting the leucopenia of the sulfonamides.

The following case reports show the value of the iron nucleotide (Ironyl) in an almost fatal case of agranulocytosis which may have been precipitated by sulfonamide therapy and three additional cases showing a quick correction of the leucopenia incident to sulfonamide therapy.

Recently, the experiment of Spicer, et al, showed that agranulocytosis, leukopenia and hypocellularity of bone marrow will develop in rats fed a purified diet with sulfaguanidine and sulfasuxidine. This blood

PATIENT Mrs. A. Fannie Bronx Hospital.

DIAGNOSIS Agranulocytosis following administration of 45 gr. of sulfanilamide preceded by twelve 7½ gr. capsules of salyprin.

BLOOD EXAMINATIONS

Date	Ironyl started 4 ampoules daily								
	2-25-39	2-26	2-27	2-28	3-1	3-2	3-3	3-4	3-6
Hemoglobin	77	72				76			
Erythrocytes	4,300,000	3,260				4,500,000			
Color Index									
Leucocytes	370	2,250	830	1,050	1,700	1,650	1,350	2,800	3,600
Neutrophils (seg. Poly)			10	15	22	16	13	10	30
Eosinophiles	37								
Basophiles									
Band Forms			40	31	14	6	11	8	8
Lymphocytes	977		46	51	50	74	66	74	60
Monocytes			3	3	10	3	6	8	2
Abnormal Cells			1 Turk		2 Plasma	1 Plasma	2 Turk	2 Plasma	

BLOOD EXAMINATIONS (cont.)

Date	Ironyl cont. 4 ampoules daily					2-26-39 In attempt to do differ 6 lymph and no polys found.
	3-7-39	3-8	3-9	3-11	3-13	
Hemoglobin						
Erythrocytes						
Color Index						
Leucocytes	4,000	5,100	6,300	5,800	5,000	
Neutrophils (seg. Poly)	35	44	55	48	67	
Eosinophiles						
Basophiles						
Band Forms	11	6	8	7	2	
Lymphocytes	50	47	32	37	29	
Monocytes	1	3	5	8	2	
Abnormal Cells						

Patient received six transfusions, of 300 cc. each, two transfusions before the onset of Ironyl therapy, each ampoule of Ironyl representing 60 mg. of iron adenylate. 36 ampoules were administered over a period of nine days. She had in addition 184 units of Lilly concentrated liver extract.

Patient had no untoward reaction of the Ironyl injections administered intra muscularly.

discrasia was prevented or successfully treated with whole dried liver or with certain liver extracts. Thus if we correlate our factors we find that adenylic acid, or substances containing adenylic acid, have both clinically and experimentally exercised a correctional influence on leukopenia and its associated disturbances.

The clinical employment of adenylic acid as a circulatory vitamin can thus be established. It has now been relatively widely used without evidence of toxic manifestations other than fleeting vasodilator effects and slight dizziness. In adenylic nucleotide we now have an additional component of the B complex whose physiological properties will doubtless find new fields of application.

The following case reports are of interest not only for the response to the pathologic condition, but also as evidence of the clinical use of adenylic acid as an iron salt in relatively large doses.

The patient, Fannie A., age 26, married, seen at Bronx Hospital, gave the following history on admission.

Three weeks prior to admission, the patient had a sore throat and was treated at home with Salpyrin, twelve capsules containing $7\frac{1}{2}$ grains each. Two days prior to admission she complained of a sore throat again, had chills and a rise in temperature to 105° . On examination, a membranous exudate was seen on both tonsils. Diphtheria culture was negative but a throat smear showed streptococci. She therefore received at home, within twenty-four hours, 45 grains of sulfanilamide by mouth in divided doses, and 20 cc of $2\frac{1}{2}\%$ Protosol solution, intramuscularly, in two doses. Her temperature rose, however, the next morning (two days after beginning of illness) to 106.4° . The patient complained of nausea and vomiting, and was hospitalized.

Examination on admission revealed a restless, young, female, acutely ill, with small patches of exudate on both tonsils. This exudate was soft, grayish in appearance, and easily removable. Cervical glands were enlarged and tender. Temperature 105.8° , pulse 120, respiration 26.

The outstanding feature on admission was a white blood count of 370 cells with 3% polys and 97% lymphocytes and a 77% hemoglobin with a red blood cell count of 4.3 million. The following day no polys were seen in the blood smear. Two days later a sternal puncture was carried out showing a typical hypoplastic type of agranulocytic marrow—71% lymphocytes, 2% plasma cells, 5% reticular cells and 22% granulocytes, showing toxic granules. Following two blood transfusions, her white blood count was 830 cells with 10% neutrophils, 40% band forms, 46% lymphocytes and 3% monocytes. On the fourth day, patient became markedly jaundiced and appeared toxic. Liver and spleen, however, were not enlarged. White blood count was 1050 with 15% polys, 21% band forms, 3% monocytes and 51% lymphocytes. Consultation with Dr. Ruskin confirmed the diagnosis of *agranulocytic angina*.

Patient's treatment consisted of almost daily blood transfusions (six in a period of nine days) during which 2300 cc of citrated blood were administered, injections of Ironyl ampules every four hours to a total of thirty-six ampules, and 134 units of Lilly Concentrated Liver Extract in two-units per cc dosages. Her condition improved, jaundice gradually disappeared,

and white blood count continued to rise until a sternal puncture taken on the ninth day showed active regeneration of all bone marrow elements. She was discharged on the eighteenth day after admission with a white blood count of 7475 showing 56% neutrophils, 31% lymphocytes, 6% monocytes and 7% young forms. One week later the white blood count was 8300.

Six months later her white blood count was 10,800 with 64% polys, 30% lymphocytes, 6% monocytes and the hemoglobin was 98% with a red cell count of 5.1 million.

Patient shows complete recovery and is feeling well.

Aside from the blood picture, the change in clinical well being was striking after the onset of Ironyl therapy. The appetite improved, the patient began to feel alert and stronger and the jaundice receded.

Barbara L., female child, age 4, had been treated in April, 1939, for three weeks for acute otitis media and had been receiving three grains of sulfanilamide every four hours from the onset of the illness. The leucocyte count, which had ranged between 9,400 and 7,200, suddenly fell to 3,200. Sulfanilamide therapy was stopped. The ear signs indicated a progression of the otitis and early mastoiditis. Iron adenyate (Ironyl-Squibb) was started. The patient received five daily doses. On the third day, the leucocyte count returned to 9,400 with 52% polynuclear cells and a mastoidectomy was performed. Sulfanilamide therapy was resumed collateral with the Ironyl administration for the first three days post-operatively and was followed by uneventful recovery.

PATIENT Mrs. O. A. C. St. C. Hospital

DIAGNOSIS Streptococcal sore throat
Sulfanilamide therapy started leukopenia corrected by
Ironyl injections

BLOOD EXAMINATION

Date	4 22 1941	Twenty four Hours After Ironyl	2 28 1941
Hemoglobin	88%		
Erythrocytes	4 300 000		
Color Index	1.0		
Leucocytes	2 500	5 500	8 600
Differential			
polys	36%	52%	72%
lymphs	50%	34%	25%
monos	6%	5%	
eosins	3%	7%	1%
myelocytes	5%	2%	

APRIL 23 1 Ironyl — Blood count
APRIL 25 1 Ironyl
APRIL 27 1 Ironyl

Mrs. O. A. C., patient at the St. Catherine's Hospital. The patient was seen in April, 1941, by Dr. Canaba for treatment of a streptococcus sore throat. She received sulfanilamide 15 grains every four hours for two days. A blood count taken April 22, 1941, on the third day of the disease, showed a leucocyte cell count of 2,500 polynuclears 36%, lymphocytes 50%, mononuclear 6%, eosinophiles 3%, myelocytes 5%. Iron adenyate therapy was instituted. She received daily injections of (Ironyl-Squibb). Twenty-four hours later her leucocyte count went up to 5,500 with

52% polynuclears and on February 28, 1941, her leucocyte count was 8,600 with 72% polynuclear leucocytes. Her clinical recovery was rapid.

Mr C, age 52, was seen in May, 1939, suffering from an acute streptococcal sore throat. He received one gram of sulfanilamide every four hours for three days with marked clinical improvement. On the third day the leucocyte count fell to 2,700 and the patient showed onset of cyanosis and slight jaundice. He received an ampoule of iron adenyate (Ironyl-Squibb) twice daily for four days. His leucocyte cell count after the fourth injection was 5,000 with normal differential count and his recovery was quite complete at the end of the week.

Mrs E L, a patient of Dr Carraba at the B R Hospital was admitted with the diagnosis of bronchopneumonia on January 2, 1939. Her white blood count on that day was 8,100 leucocytes with 61% neutrophils. Sulfapyridine therapy was not started because of the low leucocyte count. Iron adenyate (Ironyl-Squibb) therapy was instituted on January 6 followed by a rise in leucocyte count to 12,650. Sulfapyridine therapy was begun and iron adenyate injections continued collaterally for six days. The succeeding leucocyte counts ranged 20,000, 25,650, 13,000, 19,350. The patient made a rapid uneventful recovery. Pneumococci were not found in the sputum and the case was considered as influenza bronchopneumonia.

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Considerations on the Diagnosis of Large Gastric Ulcers and Implications as to Treatment

By

FREDERICK STEIGMANN, M.S., M.D.
CHICAGO, ILLINOIS

FOR many years it has been the conviction of a few clinicians and particularly of those at the Mayo Clinic, that every gastric "ulcer" should be looked on with concern and watched closely. The Mayo Clinic view has been also, that ulcers larger than a quarter are particularly likely to be malignant. This was

shown statistically by Alvarez and MacCarty (1) and others (2). This view was only slowly accepted, and even today many patients are dying of cancer of the stomach because for months they were treated on the assumption that any crater-like lesion seen in the stomach should be looked on as benign (3) until it has been proved otherwise.

Because opinion in the matter does not seem yet to have entirely crystallized, I wish here to report con-

*From the Cook County Hospital, Departments of Therapeutics and Internal Medicine and the University of Illinois College of Medicine Department of Internal Medicine.

clusions derived from a study of over two hundred cases of large gastric ulcer seen at the Cook County Hospital in the last ten years. The patients with these ulcers represent about a fifth of those with gastric ulcer seen in the Clinic and the Hospital during the time specified. Most of them had repeated X-ray examinations, follow-up studies, repeated Ewald-meal tests, and stool examinations.

Every patient in whom a large gastric niche was discovered on X-ray examination, and who was thought by the roentgenologist to have a benign ulcer, was put on an intensive medical regimen. Some patients were subjected to a continuous colloidal aluminum drip for 8-10 days. If no clinical and X-ray improvement was noted within 3-4 weeks, exploratory lapa-

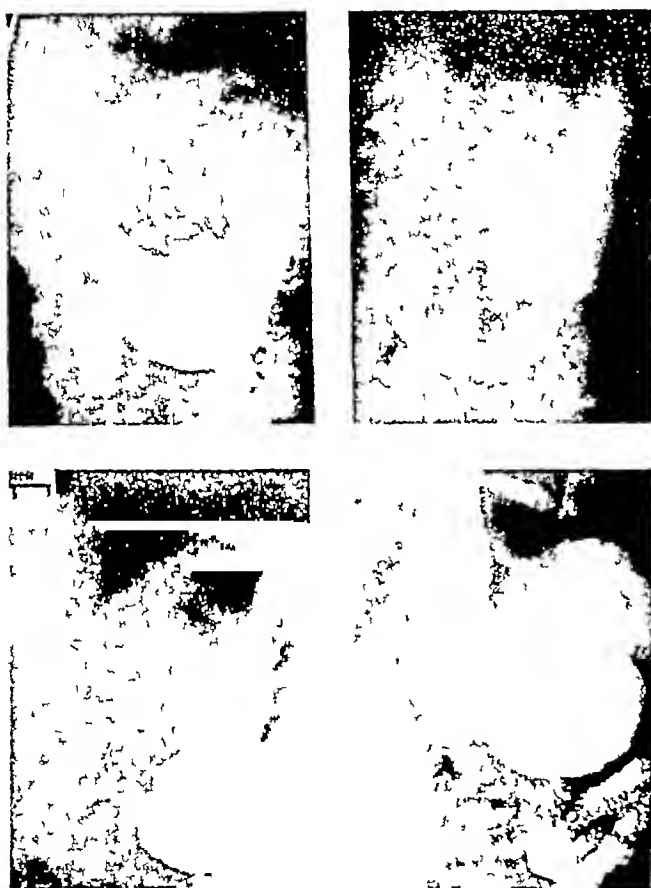


Fig 1 Showing two large irregular benign gastric ulcers (A and B) which were diagnosed as ulcerating carcinomas on X-ray, and two comparatively smooth niches (C and D) which were diagnosed benign on X-ray and proved to be malignant on histologic examination.

rotomies were performed. In recent years surgery was resorted to in many cases, even when the roentgenologist reported the ulcer benign but the gastroscopist called it malignant. At times, when a large irregular crater was called malignant by the roentgenologist but benign by the gastroscopist, the patient was put on the trial medical regimen for 3-4 weeks.

The results to date cause my colleagues and me to question the correctness and value of the signs and symptoms thought by some to be typical of benign or malignant ulcers. Indeed, even the progress and clinical course of a patient with large gastric ulcer is at times no criterion to be relied on. As one sees more of these cases one realizes that there are no

symptoms, signs, laboratory tests, X-ray or gastroscopic findings which will determine the nature of a large gastric ulcer. The response to medical management is often misleading. At times, even the surgeon and pathologist cannot differentiate a benign from a malignant gastric ulcer, and only histologic examination of the resected lesion will give the exact diagnosis. However, it must be emphasized that the histologic sections have to be taken from various parts of the large ulcer crater (walls, floor, and margins) before a definite opinion can be given. Failure to follow this precaution has resulted in patients dying of a carcinoma several months after the resected lesion was reported benign.

X-ray findings are supposed to be 95 per cent correct in the diagnosis of peptic ulcer. In cases of large gastric ulcer, however, diagnostic errors are made in both directions (4), i.e., lesions diagnosed as benign by X-ray may be malignant, and vice versa (Fig 1). Similarly, certain clinical and laboratory data which supposedly point to the one or the other type fail us in the case of the large gastric ulcer.

When we checked some current theories in regard to the characteristic symptoms of benign gastric ulcers, we found the following fallacies when these theories were applied to diagnosing the large ulcers of our series.

(1) Long duration is usually assumed to point toward a benign lesion. However, in our series of large gastric ulcers which proved to be malignant, there were several patients who gave long histories of indigestion. On the other hand, a history of less than one year's duration of gastric symptoms was obtained in almost 20 per cent of proved large benign gastric ulcers. This discrepancy in the history is usually due to differences in pain tolerance. Moreover, the patients seen in our clinic being mainly of the lower social strata, may possibly have neglected "milder" gastrointestinal symptoms. Since, however, similar observations have been made in other clinics, it is safer to assume that with any class of patients the duration of symptoms in the presence of a large gastric ulcer is not a reliable point in differential diagnosis. Similarly, periodicity of symptoms was found in both cases of benign and malignant ulcers.

(2) The age of the patient is of little help in the differential diagnosis of large benign and malignant gastric ulcers. Eighty-two per cent of the patients with large benign gastric ulcer were over 40 years of age, while during the same period several instances of carcinoma with ulcer-like niches were found in patients below 40.

(3) The type of pain, and its response to food, alkali, or vomiting, were not of much diagnostic value, since similar complaints were obtained from patients with both types of lesions. About four per cent of the patients with benign lesions reported no relief from any kind of medication, while, on the other hand, several cases later diagnosed as carcinomas secured relief for short periods on an alkali regimen. Furthermore, large gastric ulcers may cause pain which is more persistent and not quite characteristic of the ulcer syndrome, in that remissions become rare and usually effective measures are found inadequate. The pain produced by large ulcers is best explained by Rivers and Day (5) who state that large ulcers which progress beyond the confines of the bowel invade

tissues guarded by spinal sensory nerves. The pain is then projected over the peripheral distribution of the involved nerves, thus changing and distorting the original syndrome to such an extent that malignancy is suspected. This non-typical pain together with a history of short duration in an individual of carcinoma age is frequently responsible for the fact that many cases of large gastric ulcer are diagnosed as cancerous.

(4) Weight loss, anorexia, and weakness are common symptoms in our series of benign gastric

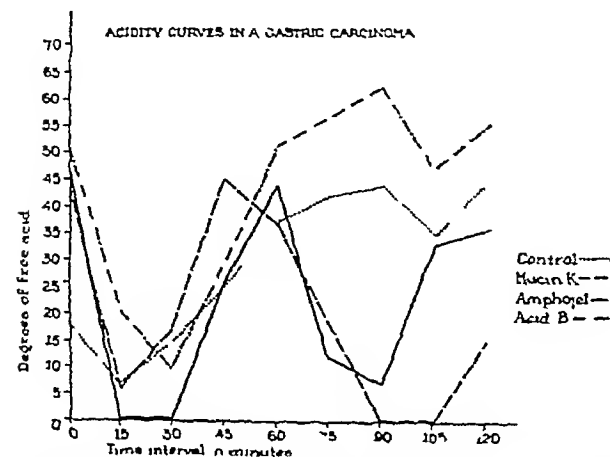


Fig 2 Graph showing several acidity curves in a patient with a large ulcerating carcinoma in the pars angularis

ulcers, and could not serve as differential diagnostic points. In several instances loss of weight running up to 40 pounds was recorded.

(5) Hematemesis, melena, and anemia were also prominent symptoms in our series, but these again could not be used in differential diagnosis of ulcer and carcinoma, since these symptoms occurred in both conditions.

(6) Free acid values above 40 degrees are usually regarded as pointing to benign lesions. We found, however, that only 30 per cent of the large ulcers had an acid value of above 40 degrees while 33 per cent had free acid below 20 degrees. In seven per cent of the cases achlorhydria was found. In contrast to the above, cases with carcinoma of the stomach may frequently show hyperchlorhydria (Fig 2).

(7) The continued presence of blood in the stool is considered indicative of malignant ulceration. The disappearance of blood on medical management suggests a benign lesion. In our series both types were met, i.e., some benign lesions continued to show chemical blood on treatment, while in others the blood disappeared. However, in a few instances of malignant ulceration, the stools became free of blood on medical treatment.

(8) The various X-ray signs described as differentiating a benign from a malignant gastric ulcer refer particularly to the size of the ulcer, its depth, its relation to the wall of the stomach and the rugal pattern, its location, and secondary signs (such as incisura opposite the ulcer, pylorospasm, or pain on pressure). Increase or decrease in size also are diagnostic points. In cases of large gastric ulcer, however, most of these points fail as diagnostic criteria mainly because of the distortions that occur in these lesions.

The size of the niche is of significance in differentiation. To be sure some of the largest ulcers are benign while some carcinomatous ulcers are rather small (Fig 3). Still, a large niche should make one more cautious as a malignancy masquerades more frequently as a large than as a small gastric ulcer.

The depth of the crater is an unreliable differential sign, as it is frequently modified by edema or infiltration around the lesion, or miscellaneous debris in the floor of the ulcer. Some benign lesions show marked depth with ragged and irregular margins, while malignant ulcers appear with comparatively shallow craters and smooth margins.

Benign gastric ulcers appear as if sculptured on the wall of the stomach, extending beyond the normal confines of the gastric lumen. Due to the chronicity and large amount of swelling and induration of the margins of the craters, many of these large lesions appear as if arising in a filling defect beneath the level of the lesser curvature, thus giving the impression of a halo about them. These were, hence, diagnosed as malignant. This process explains why, in large ulcers, the radiation of rugal folds towards the crater may not be clearly demonstrated, and why the margin of the lesion appears effaced, with a seeming disappearance of the mucosal pattern.

The location of the lesion seems to be a more dependable X-ray sign in cases of large gastric ulcer. In our series of proved large benign craters, over 90 per cent were found in the pars media, i.e., above the angulus and below the cardia, few in the antral region and none on the greater curvature. However, a few malignant ulcers were met in the pars media also. Most of the diagnostic errors occurred with lesions in the antral region.

Incisuras opposite the lesion were not seen in many cases of large gastric ulcer. They are apparently less



Fig 3 Showing a large benign gastric ulcer (A), and a small ulcerating carcinoma (B)

commonly associated with large than with small lesions. On the other hand, in two instances, pseudo-incisuras opposite large malignant craters were found due to pressure on the greater curvature by bands of infiltrated omentum (Fig 4).

Pylorospasm was found in a small percentage of large gastric ulcers. At times the spasm was so marked and persistent that during the entire X-ray examination the whole antrum below the crater was obliterated, giving a picture of a diffuse infiltrating



Fig 4 Showing Pseudo incisuras in cases of ulcerating carcinoma caused by bands of omentum which were pulled upward towards the lesser curvature by the carcinomatous masses

carcinoma that had destroyed the lower third of the stomach (Fig 5)

In almost 10 per cent of our cases of benign gastric ulcers, an associated ulcer of the duodenum was found. Such a combination was not observed in any case of malignant ulcer. Hence the presence of a duodenal lesion may be a helpful differential point.

Pain on pressure was found in most of our cases with large gastric ulcers, whether benign or malignant, and hence cannot be used as a differential point. As stated above, the pain seems to be due to perforation of the lesion into neighboring viscera with involvement of the spinal sensory nerves.

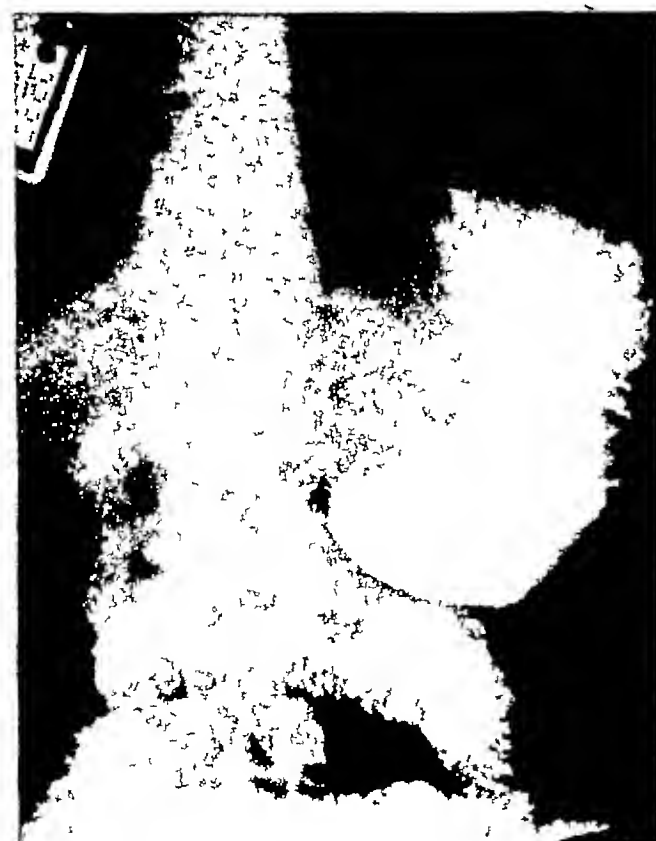


Fig 5 Showing marked antral spasm from a benign gastric ulcer on the lesser curvature (pars media) leading to a diagnosis of possible pyloric carcinoma

The appearance of a "tobacco pouch" formation due to an excessive shrinking of the lesser curvature resulting in the approachment of the pyloric area to the angulus, strongly supports the diagnosis of a benign lesion. The "tobacco pouch" stomach is frequently associated with delayed emptying or actual retention (Fig 6).

Many of the large benign craters showed diminution in size on medical regimen. Similar observations have been made by us and others (6) in cases of malignant lesions. On the other hand, some benign craters do not heal. Hence, the decrease in size of the lesion as a criterion of benignancy may at times prove hazardous from the viewpoint of prognostication.

(9) The advent of the gastroscope was hailed as a great aid in the differentiation of benign from malignant ulcers. In general, it fulfilled the hopes, but it is not infallible. Errors are made in both directions. Schindler (7) describes the gastrosopic appearance of a benign ulcer by picturing it as a round crater with sharp, somewhat irregular edges. The malignant ulcer he described as "usually rather large, and sur-



Fig 6 Showing two representative pictures of the so-called tobacco pouch stomach caused by an excessive shrinkage of the lesser curvature which pulls the pylorus towards the crater

rounded by a high dark red wall of variable thickness that apparently does not extend into the adjacent pale tissue. The floor is irregular, covered with pieces of necrotic tissue and may be dirty gray, greenish-gray, brown, reddish, or violet in color. The edge of the floor is not as sharp as in a benign ulcer."

The above characteristics of benign and malignant ulcers seem to disappear when there are large craters. In our cases good gastroscopists erred in the diagnosis of such large ulcers by calling benign lesions carcinomatous and vice versa. It seems that in cases of large gastric lesions the signs differentiating a benign from a malignant lesion are as undependable in gastroscopy as in roentgenology.

Schindler (7) contends that it is easier to differentiate benign and malignant ulcers gastrosopically than by examining in the gross the resected specimen. One can agree with this contention provided that one of Schindler's skill does the gastroscopy.

Palmer (8) states that no criteria are pathognomonic of a benign lesion, unless it be the roentgenologically and gastrosopically observed and proved complete healing of an ulcer. From our observations we agree with the first part of this statement, but ex-

ception has to be taken to the latter since even it may prove fallible, as observed in the following report

CASE REPORT

J S, a 57 year-old Negro, had had gastro-intestinal disturbances for two and one-half years when he first came under the observation of one of the city's clinics. Complete examination and laboratory tests at that time were essentially negative, except for the following X-ray report

"Fluoroscopically, the stomach appeared normal. The duodenal bulb appeared deformed throughout the fluoroscopic observation. There was tenderness over the bulb and the antrum of the stomach. The films show a normal-appearing stomach with a deformity of the duodenal bulb due, I believe, to an old ulceration with some X-ray evidence at the present time of activity." The patient was put on a peptic ulcer regimen, but failed to improve.

A second X-ray examination five months later resulted in the following report "The stomach appeared normal throughout the fluoroscopic observation. The duodenal bulb visualized immediately without spasm. It was again found to be deformed from an old ulceration and scar tissue contraction. Considerable local tenderness was found over the bulb."

Because of the poor healing of the lesion, operation was advised. The patient refused operation. He entered the Cook County Hospital three months later complaining of mild pain in the epigastrium, usually occurring in the afternoon without any apparent cause. The patient was only slightly relieved by antacids. Some of the worse pain would occur in the early morning hours. Food would relieve the pain at times, and at other times would not influence the pain at all. There had been a weight loss of 10 pounds in the past few weeks.

The physical examination at this time revealed a well-developed and fairly nourished colored male. Except for marked epigastric tenderness, there were no other physical findings. Laboratory tests revealed a trace of albumin in the urine, achlorhydria, hemoglobin of 60 per cent, RBC of 4,500,000, and WBC of 11,800. X-ray of the stomach—May 27, 1941—was reported as negative for any pathology in the stomach or duodenum.

Gastroscopy on June 4, 1941, gave the following results "No acid in aspirated gastric contents, a most unsatisfactory examination of a stomach in which an ulcer on the anterior wall of the antrum was present. The character, however, could not be determined."

Because of the gastroscopic report the patient was fluoroscoped on June 7. At this time the roentgenologist reported "There is a small gastric ulcer present on the lesser curvature of the pars media just at the junction of the pars pylorica."

The patient was regastroscooped two weeks later. The following report was given "Benign ulcer on the lesser curvature of the antrum. The rest of the stomach is normal."

The patient was put on an intensive ulcer management on which he seemed to feel fairly well. He was regastroscooped two weeks later and the following report was obtained "A beautifully healing benign ulcer of the anterior wall of the antrum on the lesser curvature."

The patient was regastroscooped two weeks later. The following opinion was given "Healing ulcer of the anterior wall of the antrum."

X-ray examination at this time—July 12, 1941—gave the following report "The stomach emptied rather rapidly. There is a rather constant incisura on the greater curvature of the stomach in the region of the angulus. This may be a secondary sign of an ulcer on the opposite side. However, an ulcer crater is not demonstrated."

The patient was then discharged from the hospital to the Gastro-Intestinal Follow-Up Clinic. There he was seen every two weeks. In spite of being on a bland ulcer diet, antacids, antispasmodics, he never felt completely well. Because of this, surgery was again advised but re-

fused by the patient. X-ray examination on September 20 failed to show a lesion. Gastroscopy on September 21, 1941, was reported as follows "A puckering scar extending into lesser curvature of the antrum in an otherwise normal stomach."

The patient continued under medical observation but no improvement was noted, and he began to show weight loss. In December, 1941, the patient was admitted to the hospital for re-examination. Again no free acid was found in the gastric contents.

X-ray examination now gave the following results "There is a rather constant irregular area of radiolucency in the pars pylorica of the stomach with a rather constant incisura on the greater curvature in this region. The findings may possibly be on the basis of an old gastric ulcer. However, a malignant process must be ruled out."

At this time the following report was obtained from the gastroscopist "The pylorus in its entirety was seen. Two large rugal folds converged behind the angulus. On the distal side of the angulus, at the lesser curvature, an ulcer with a gray crater could be seen in profile. This ulceration could not be visualized in its entirety because it was situated on the lesser curvature of the antrum. The part that could be seen had a smooth and edematous edge and appeared benign. From a gastroscopic point of view, this patient should go to surgery because of (1) Progressive distortion of the lower end of the stomach, (2) Existence of an ulcer after adequate medical management, (3) Absence of hydrochloric acid. At the operation a carcinoma of the lesser curvature of the stomach was found with glands all along the curvature high up towards the diaphragm. A few metastatic nodules were found in the liver. A subtotal resection was performed."

The surgical pathologist reported "Stomach previously opened along the greater curvature 16 cm in circumference and 11 cm longitudinal. Involving the lesser curvature and extending for 2 cm over the anterior and posterior wall is a huge defect measuring 6.3 x 4.5 cm. The edges of this defect are raised, firm, reddish grey. The base is light tan, grey and firm. Serosal defects are slightly thickened and pinkish tan. Perigastric lymph nodes up to 2.5 cm. Section of stomach reveals an infiltrating mucus-producing adenocarcinoma. No evidence of metastases seen in a regional lymph node."

The patient made an uneventful recovery from the operation and left the hospital December 31, 1941. Since the operation he has been having less epigastric distress, and thus far seems to be going along pretty well.

SUMMARY

From the above discussion it is evident that large gastric ulcers are significantly more often malignant than are smaller lesions. The hazards confronting the clinician, roentgenologist, and gastroscopist in the differential diagnosis of large gastric ulcers are great and this fact needs to be re-emphasized. The results of this study of large gastric ulcers, extending over a period of 10 years, support similar previous reports (9) showing that there is nothing in the history, physical examination, laboratory tests, findings on X-ray study gastroscopy, or in the results of medical treatment which will unfailingly differentiate a benign from a malignant gastric ulcer. In some cases only the histologic examination of the excised lesion will lead to correct diagnosis.

The therapeutic implications of the foregoing considerations would seem to be clear. To the writer, as to many others (10), the observations here reported suggest the advisability of resecting every large gastric ulcer. As pointed out in a previous paper (11), resection of large gastric ulcers is advisable not only

because of the danger of misdiagnosing a malignant lesion as benign, but also because the complications of these large gastric ulcers make them in a way malignant when they are histologically benign. We advise surgery for large gastric ulcers even though we are aware of Bloomfield's (12) conclusion that errors in differential diagnosis do not exceed the mortality rate of resection. This conclusion seems inapplicable to the clinic where I work where the mortality from operation is not high.

For years I followed the plan of closely observing our patients with large gastric ulcers until the lesion was completely healed. The results, however, were not entirely satisfactory inasmuch as even when the lesion was not malignant, we frequently saw recurrences and complications after apparent complete healing and finally we often had to operate. From such observations, I would hesitate to say that there is such a thing as complete healing of a large gastric ulcer on medical treatment. The excellent paper by Palmer (13) and his associates supports this view. Considering, therefore, the complications that may arise from large gastric ulcers, even when they are benign, and the possibility that they may be carcinoma-

matous, it seems to me that one can never rest content until such a lesion is resected.

CONCLUSIONS

1 Even though all large gastric ulcers are not malignant, many of them are and, hence, it is dangerous to treat them medically.

2 There are at present no pathognomonic signs to differentiate a large benign gastric ulcer from an ulcerating carcinoma or an ulcer which is becoming malignant.

3 The only way in which the nature of some lesions can be determined with certainty is by histologic examination.

4 Large benign ulcers usually heal poorly, and often complications occur which in the end, force the patient to be operated on.

5 It would seem then that as soon as a large ulcer is found, the best treatment is excision. This will not only work a cure where other methods fail but it will prevent complications and it may save the patient's life in those many cases in which carcinomatous changes are present.

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Prolapsed Gastric Mucosa: Roentgenologic Demonstration of Ulcer Crater in Prolapsed Polypoid Mucosa

By

A. MELAMED, M.D.

and

ROBERT I. HILLER, M.D., F.A.C.S.

MILWAUKEE, WISCONSIN

THE diagnosis of prolapsing gastric mucosa is occasionally made after roentgen examination of the gastro-intestinal tract, but the number of cases recorded in the literature is quite small. Most of the recorded cases have been confirmed by surgical exploration. Recently Rubin (1) reported a case of prolapsed polypoid gastric mucosa with malignant change. The following cases have been reported:

Schmeden (2), 1911	1
Ehason and Wright (3), 1925	1
Ehason, Pendergrass and Wright (4), 1926	2
Meyer, K. A. and Singer (5), 1931	1
Meyer, W. H. (6), 1935	1

Pendergrass and Andrews (7), 1935	3
Rees (8), 1937	4
Bohrer and Copleman (9), 1938	1
Aicher and Cooper (10), 1939	4
Rubin (1), 1942	1

19

Although we have recently observed four cases of prolonged gastric mucosa, only one has been verified by surgical exploration. This case presented some unusual pathological and roentgenologic findings.

CASE REPORT†

History (116923) P. S., married white female, aged 39, was admitted with the chief complaint of marked

*From the Department of Radiology and Department of Surgery, Mount Sinai Hospital, Milwaukee, Wisconsin.

†This patient was referred by Dr. L. Kaufman.



Fig 1 Filling defects occupying prepyloric and antral portions of stomach and adjacent portion of duodenal bulb. Static area of barium sulphate (A) in midst of filling defect corresponds to location of large ulcer crater in the prolapsing polypoid gastric mucosa

weakness. For three months preceding entrance to the hospital, patient had noted black, tarry stools. On occasions there was bloating and belching shortly after meals. A physician was first called to treat injuries to her cheek produced by a fall during an episode of faintness and dizziness. The patient admitted some loss of weight, but could not state the exact amount.

The past history was essentially negative except for history of frequent and severe headaches, accompanied by nausea and vomiting since the age of 18 years.

Examination. The outstanding feature presented by the patient was a striking pallor. She lay quietly in bed in no acute distress. Discoloration and puffiness of the left cheek were present. Abdominal examination showed no evidence of tenderness, rigidity, distension, fluid, masses nor enlarged organs. The blood pressure was 130/68, pulse 104, temperature 99.4° F. The impression on admission was a bleeding peptic ulcer with marked secondary anemia. Other possibilities, such as gastro-intestinal malignancy, multiple polyposis of the stomach and ulcer in a Meckel's diverticulum were considered.

Laboratory Data. The blood determinations on admission to the hospital were as follows: Hemoglobin, less than 3 grams, red blood cells, 1,730,000, white blood cells 15,650, polymorphonuclear cells, 87%, lymphocytes, 10%, eosinophiles, 1%, monocytes, 1%, polychromatophilia, poikilocytosis, anisocytosis and hypochromia. The blood Kline reaction was negative. The stools were strongly positive for blood.

Course. After a series of transfusions the patient's red blood cell count rose to 4 million. The red blood cell count, however, fell sharply as soon as the transfusions were discontinued. It became evident that active bleeding was occurring and surgical intervention was deemed necessary. Roentgen examination of the gastro-intestinal tract was performed in an attempt to locate and identify the lesion responsible for the hemorrhage.

Four days after admission to the hospital, barium meal examination showed evidence of a filling defect measuring approximately 5 cm. in diameter in the antral and prepyloric portions of the stomach. The filling defect would at times be seen to occupy the region of the base of the duodenal bulb (Fig 1). Mucosal changes were noted but the changes were not those of an infiltrative type of lesion. A ring-like static area of barium was observed in the prepyloric region (Fig 1) when the filling defect was found to extend into the duodenal bulb. The prolapsing lesion was observed in both the prone and upright positions. At the four hour examination, a slight amount of barium mixture was still present in the stomach. The

roentgen appearance of the abnormality described in the distal portion of the stomach and in the adjacent portion of the duodenal bulb was more consistent with the diagnosis of a prolapsing gastric polyp. Whether the polypoid lesion was benign or malignant could not be definitely determined from the roentgen examination. The size of the prolapsing lesion was almost too great to favor the diagnosis of prolapsing mucous membrane, this lesion, however, could not be definitely excluded.

On February 24, 1942, the patient was submitted to surgery. A midline incision was made in the epigastrium, and after a freely movable mass was palpated in the stomach, the stomach was opened transversely, in the antral region. "A polyp with a large ulceration followed by a prolapse of mucous membrane of stomach originating from the posterior gastric wall in the region of the fundus of the stomach was removed by excision (Fig 2)." The entire lesion measured about six inches in length. The mucous membrane was sutured with a double layer of dulox stitches. The opening in the stomach was then closed in two layers with dulox surgical gut. The abdomen was closed with interrupted steel wire sutures through the peritoneum and fascia. Clips were used on the skin.

The fixed specimen measured 9 x 6 cms. and consisted essentially of reduplication of a giant gastric fold of mucosa and submucosa. The gastric mucosa was markedly hypertrophied and was generally intact except for two ulcerations. The larger of the two ulcerations measured 3 x 1.5 cms. The edges of the ulcers were overhanging and the bases were covered with soft, yellowish exudates.

Microscopic examination (Pathological Report by Dr Norbert Enzer) showed hyperactive mucous-secreting glands which lined the broad fold. The mucosa was destroyed in two fairly well circumscribed areas. The bases

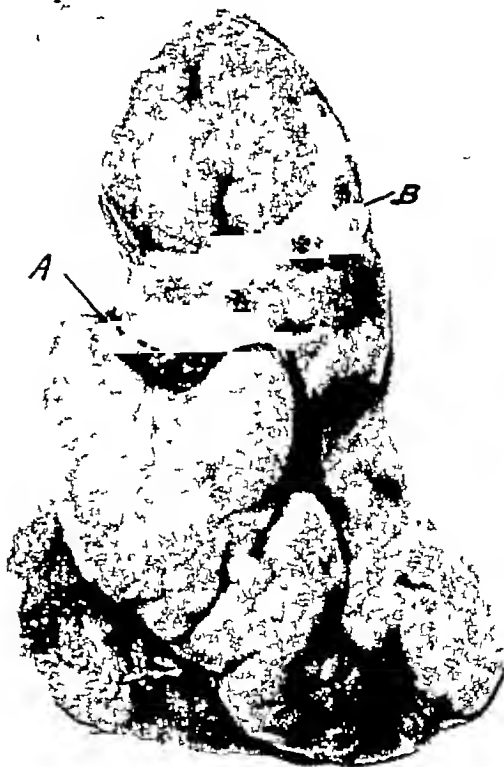


Fig 2 Surgical specimen measuring 9 x 6 cms showing marked hypertrophy of gastric mucosa. Large ulcer crater (A) measures 3 x 1.5 cms. Smaller ulcer situated distally (B)

of the ulcers were covered with thin layers of leucocytic and fibrinous exudates. The stalk of the prolapse was made up of a diffuse overgrowth of fibrous tissue which was infiltrated by masses of all types of inflammatory changes.

The patient made an uneventful recovery and was dismissed from the hospital on March 7, 1942, about 23 days after admission or 11 days following surgery.

A subsequent barium meal examination performed on March 16, 1942, approximately three weeks after surgery, showed no evidence of prolapsing gastric mucosa. There was a slight irregularity in the outline of the lesser curvature of the stomach which was undoubtedly the result of the operative procedure. The patient has been in good health since the surgery was performed.

ETIOLOGY

A few theories have been advanced to explain the hypertrophy and mobility of the gastric mucosa in this condition. In 1925, Elason and Wright advanced the theory that hypertrophy of the gastric mucosa, due to pre-existing chronic inflammatory irritation, precedes the actual prolapse of the mucous membrane.

Rees expresses the opinion that narrowing of the pyloric ring precedes the actual changes in the gastric mucosa. The findings in our patient tend to contradict the theory of Rees, because the pylorus was found to be relaxed, freely admitting two fingers. The ability of the pylorus to permit the passage of the large prolapse confirms our impression that this relaxation was not temporary in nature.

SYMPTOMATOLOGY

The intermittent character of the symptoms is stressed in most of the case reports of prolapsed gastric mucosa. This can be readily understood when one realizes that the prolapse of the mucosa is intermittent. The symptoms emphasized are not specific and consist essentially of epigastric distress, fullness, clamp-like pains, gaseous distension, and occasionally, vomiting. The symptoms are usually most pronounced after meals.

The profuse intestinal bleeding and the resultant secondary anemia present in our case have been previously reported but are not necessarily regular accompaniments of the disease. Many of the patients present scars of previous surgery in the upper abdomen.

DIAGNOSIS

Roentgenologic demonstration of a prolapsing lesion of the stomach is practically the only reliable method of diagnosis. Definite diagnosis without X-ray confirmation would be purely conjectural.

Barium meal examination must include examination of the patient in the erect and recumbent positions. Although prolapsing gastric mucosa is usually demonstrated in the recumbent position, our proved case showed roentgen evidence of the lesion in both the erect and prone positions. Serial roentgenograms with the aid of a polygraph are of distinct value in such a condition.

Pre-operatively, roentgen evidence of at least one ulceration in the prolapsing mucosa was present in our case. Surgical removal of the lesion made possible the correlation of the roentgenologic and pathological findings. The static, pre-pyloric, initialuminal, ring-like area of barium sulphate described on the original roentgenograms when the prolapse extended into the duodenal bulb, represented the large ulcer crater in the prolapsing gastric mucosa. The specimen showed

a constriction in the region of the ulceration, the latter was evidently produced by the pressure of the pyloric contractions on the prolapsing lesion. Streaking of the contrast media seen in the duodenal bulb represented barium between the folds of prolapsed hypertrophied mucosa.

Roentgenologic differentiation between a prolapsing gastric polyp and prolapsing hypertrophied gastric mucosa is impossible. In either instance one is also unable, from the roentgen standpoint, to determine whether the lesion is benign or malignant. Further evidence of this fact is contained in Rubin's recent case report.

TREATMENT

If the lesion is of sufficient size to produce symptoms or if it is the origin of gastro-intestinal bleeding, the treatment is surgical. Small prolapses should be kept under observation especially for evidence of bleeding and subsequent increase in size. In view of the recent report by Rubin of a case undergoing malignant change, one must not take such a lesion lightly.

That the lesion has been frequently missed even with the abdomen open, is emphasized by the fact that many of the reported cases have had previous abdominal surgery, some gastric surgery. This is readily understood when one realizes that the lesion is merely a reduplication of the mucosa and submucosa and gives no sensation of mass or substance when palpated through the stomach wall. Furthermore, with the patient on the operating table in the supine position, the prolapsing mucosa slips back from the duodenum and pylorus. In our case the large mass had slipped up into the fundus where it originated and was not definitely demonstrated until the stomach was opened.

The operative procedure consists of opening the stomach and excising the mass down to the muscular coat of the stomach. The defect in the gastric mucosa is then closed and the opening through the anterior wall of the stomach is then closed in layers. Whether the incision through the anterior wall of the stomach is made longitudinally or transversely is probably a matter of personal preference. In our case an incision transverse to the long diameter of the stomach in the antrum about 2 inches from the pylorus was used. This incision is comparatively avascular.

SUMMARY

A case of prolapsed polypoid gastric mucosa, visualized by roentgen examination and verified by surgery, is presented. Severe melena arising from two ulcers on the prolapsing mucosa was the outstanding symptom. At least one of the ulcers was demonstrable on the roentgenograms.

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Multivitamin Prophylaxis and Therapy in Respiratory Diseases of the Aged

By

LESLIE L. KAY, M.D.
NEW YORK NEW YORK

DURING the past few decades much investigation has been devoted to vitamins, and considerable knowledge has been accumulated concerning their importance in the prophylaxis and therapy of many diseases. The subject of vitamin deficiency in the aged, however, has received comparatively little attention in the literature on vitamins. Only a few authors have considered it as a separate problem, and not many of us have fully realized the fact that vitamin deficiency is much more frequent in old age than perhaps in any other period of life.

REASONS FOR DEFICIENCY

I have had the opportunity to make observations on several hundred aged people in three large institutions. Although the meals served to them are wholesome, and served in sufficient quantities, I found that most of the inmates had readily apparent or hidden vitamin deficiencies. The deficiencies in most of the cases had been caused by a combination of factors. Many old people are poor eaters, many more show preference for certain kinds of food, rejecting highly nutritious food like meat, vegetables, or fruits. They give preference to liquids or semi-liquids, or easily masticated food. They seem to desire sweets or starches. We have also to consider the methods and intensity of cooking. Most old people prefer a soft diet. To make vegetables and meat as soft as they want them requires more cooking, which in turn causes the loss of a number of vitamins by prolonged heat and the loss of others in cooking water. Many of the old people are unable to chew food well, due to an insufficient number of teeth or loosely-fitting plates. There are other pathological conditions and common diseases of the old—especially is this true in connection with arteriosclerosis—which often force many old people to observe restricted diets, with resultant inadequate intake of vitamins. Finally, the greater frequencies of vitamin deficiencies in old age may be due to the body's increased demand for vitamins, because of their poor absorption or deficient utilization.

SEASONAL FACTOR

The number of old people with apparent symptoms of vitamin deficiency increases significantly toward the end of winter. This is due partly to their diet, which contains less fresh vegetables and fruit than in any other season and partly to a lack of sunshine and fresh air, imposed on them during the long, cold months spent indoors. Toward the end of winter—and the first part of spring, when the weather changes frequently—when sunshine, snow, rain and wind follow each other in an unpredictable manner, acute respiratory infections in the aged reach a high seasonal peak. It is true that influenza and pneumonia

at that special time kill a large number of inmates in the homes for the aged. They fall like dry blades of grass blown down by the wind, in spite of sulfanilamide therapy, and serotherapy and in spite of the best medical care given them. It is apparent that they have little or no resistance with which to fight these diseases. And vitamin deficiencies are certainly among the factors which cause this lowered resistance to respiratory infection.

VITAMINS A AND C

The great importance of Vitamin A, the "anti-infective vitamin" of Mellanby, in maintaining the integrity of all epithelial tissues makes obvious the fact that the lowered resistance of the respiratory epithelium to infections is often in direct consequence to deficiencies in Vitamin A. As a matter of fact, in Vitamin A deficiency the upper respiratory tract, particularly the nasal passages, trachea and bronchi, shows a transformation of the lining epithelium into a stratified epithelium of flattened cells which undergo extensive keratinization. The content of Vitamin A in lung tissue varies directly with the amount in the ingested food, and therefore it is possible that deficiency in this vitamin may predispose to the development of pulmonary tuberculosis and other lung diseases in man (Wright). The role of Vitamin C in preventing respiratory disease is not less important. Research in Vitamin C has clearly shown that in pneumonia, influenza, tuberculosis, bronchitis, corvza, and sinusitis—in a word, nearly all of the respiratory infections which take their toll among the aged—Vitamin C concentration in blood and tissues is abnormally low. Though this consideration suggests only the use of these two factors in the prophylaxis of respiratory diseases—after having realized the frequency of anorexia and other common signs of Vitamin B deficiency I decided upon using a multivitamin preparation in my studies.

CLINICAL EXPERIMENT

For the experiment 25 patients were selected from the 75 inmates in the United Home for Aged Hebrews in New Rochelle, N. Y. I particularly selected those who showed the most apparent vitamin deficiency syndromes. Seven of the patients suffered from chronic respiratory disease, one of the seven also had generalized erythrodermia. These seven patients as well as the rest of the 25 were more or less markedly arteriosclerotic. Three patients had arteriosclerotic Parkinson's syndrome, several had signs of arteriosclerotic heart disease, and advanced cerebral arteriosclerosis. Seventeen of these patients—68%—complained of loss of appetite. Four patients presented chronic glossitis, five were anemic, two mentally depressed and four neurasthenic. From the end of January, 1941, to the middle of June these selected 25 patients were given

vitamins for a period of time varying from one to three months, depending on clinical results obtained. The other 50 patients of the institution were considered as control. Their weight, general well-being, and the diseases they acquired were carefully checked. Each patient was given 9000 U.S.P. Units of Vitamin A, 200 International Units of Vitamin B₁, 100 gamma B (Riboflavin), 500 International Units of Vitamin C, and 900 U.S.P. Units of Vitamin D twice a day in the form of perles.*

RESULTS

The results achieved in the daily administration of multivitamin perles to the aged can be classified in two groups: prophylactic and therapeutic. The prophylactic use of vitamins proved to be highly satisfactory in the prevention of acute respiratory infections. None of the 25 patients receiving vitamins had any acute respiratory diseases from the end of January until the middle of June although during this period of time there was a mild epidemic of influenza in the home. Five of the patients who had not been receiving the perles developed the disease and two had bronchopneumonia. A great many of the inmates acquired colds, but the patients who had been receiving the perles had none of these diseases. The full significance of this result becomes evident when we consider the fact that the selected 25 inmates of this home were apparently the weakest, and therefore most liable to infection.

Therapeutic results are shown in the accompanying chart.

Case No.	Name	Age	Sex	Disease	Duration of Treatment	Comment
2	S. S.	80	F	Chronic Fibroid Tuberculosis Repeated hemoptysis Anorexia	2 1/2 Mos.	After the 10th day of treatment patient stopped bringing up blood. Her appetite and general condition improved. Gained 4 pounds.
7	H. K.	70	M	Chronic Fibroid Tuberculosis Anorexia	2 1/2 Mos.	After an initial general improvement of his appetite and weight (he gained 5 lbs.) his condition grew worse.
8	F. B.	72	F	Chronic Rhinopharyngitis Frythrodemia	2 Mos.	Her rhinopharyngitis improved. Gained 4 lbs. Her skin became paler. Desquamation reduced.
9	I. C.	72	M	Rhinitis sicca Chronic Gastritis Anorexia Neurasthenia	3 Mos.	The ulcers healed. He complained less of anorexia, burning of tongue, etc. Gained 5 lbs.
14	S. K.	69	M	Bronchial Asthma Chronic Bronchitis Chronic Myocarditis	3 Mos.	No new asthmatic attacks had occurred since starting multivitamin therapy. Appetite improved. Gained 4 lbs.
23	H. C.	80	M	Chronic Bronchitis Chronic Gastritis	2 Mos.	Good results.
25	L. L.	72	M	Chronic Fibroid Tuberculosis	1 Mo.	Appetite improved. Gained 2 pounds.

Among the cases presented No. 19 deserves the most attention. The 83 year-old patient had suffered very severe asthmatic attacks for years before starting multivitamin therapy. A short time after taking vitamins he became more comfortable and stopped complaining of dyspnea. Administration of two perles daily was continued for another five months. During this time no asthmatic attack has occurred, either, but early last fall—for the first time in his life, he had a short but severe hay fever attack.

As to the other patients the therapeutic results showed that although none of the patients with Parkinson's syndrome exhibited any objective improvement, they all benefited by the multivitamin therapy, especially in appetite increase and improvement in well-being. As a matter of fact, multivitamin therapy improved the appetites of almost everyone taking the perles. In cases of anorexia and undernourishment

most striking results from multivitamin therapy were seen. Of the 17 anorexia patients, several of these also undernourished, 6 showed excellent results, 9 did fairly well, 1 only fair, and 3 showed poor results. The 25 patients kept on vitamins gained 67 pounds altogether. Some of these cases are of special interest.

Case 4 L. R., 82 years old, female, complained of nausea, burning feeling in tongue, loss of appetite, and general weakness. All of these complaints, as well as objective findings such as smooth red tongue, loss of weight, dyspnea, bradycardia, improved in less than three months, and the patient gained 10 pounds.

Case 7 C. B., 80 years old, female, suffered from loss of appetite, sleeplessness, nervousness, nausea and vomiting. She presented marked anemia, and atrophic glossitis. The patient gained 5 pounds in the first two months of vitamin therapy, and 2 pounds more in the next seven weeks. All of the symptoms disappeared.

Case 13 J. H., 85 years old, female, bed-ridden for more than a year with a fractured hip, presented a hypochromic anemia, general weakness and anorexia. After 3 months of administration of vitamins she gained 6 pounds. Her appetite improved, she became stronger and was able to walk a few steps.

It is also interesting that one of the mentally depressed patients presented a surprising change after administration of multivitamin perles. Case 1 M. M., 70 years old, male, suffered from mild confusion, depression and apathy. He complained of fatigue, weakness and loss of appetite. A few weeks after starting the multivitamin therapy he regained his appetite. At the end of the third month his mental and physical condition was so much improved that he seemed quite a new man. The favorable

results did not last long. After discontinuing the multivitamin therapy he soon started complaining of general malaise and weakness. But having taken vitamins for the past few months, he feels all right again.

In concluding this article, I have found multivitamin therapy affects the blood pressure of the aged. My observations showed that in several cases where the blood pressure was abnormally low, it tended to rise as the result of multivitamin therapy, probably in connection with the improved general condition, gain in weight, and improved appetite. This was especially noticeable in case 7, already described, where the blood pressure was raised in three months from 100/65 to 146/85. On the other hand in 3 cases where the patients suffered from hypertension the blood pressure became still higher.

Multivitamin administration in the aged benefited most of the patients to whom it was given. Although final conclusions on the basis of this small series of cases are not permissible, and although much more

*Vi-Penta Perles, manufactured by Hoffmann-La Roche, Inc. Each perle contains the vitamin values above mentioned.

clinical study must be done before conclusive statements can be made concerning the effects of multivitamin therapy on respiratory infections in the aged results of the study suggest three things

CONCLUSIONS

1 Vitamin deficiency in the aged is more frequent than is generally supposed

2 Vitamin deficiency is among the factors which play an important part in the susceptibility of the aged to respiratory infections

3 Adequate amounts of vitamins afford marked prophylactic benefits, and multivitamin therapy besides having general beneficial effects upon the aged, provides a useful weapon in our fight to prevent respiratory infections in the old people

Incidence of Intestinal Parasites in a Tropical Area of Brazil*

Figures Based on the Examination of the Stools of 2,500 Patients

By

J ROMEU CANÇADO, M D
BELO HORIZONTE BRAZIL

FEW data are available in Brazilian literature regarding intestinal parasitism in this area of the country Belo Horizonte and neighborhood (1, 2, 3) Hence the interest of this communication in which I have noted down the commonest intestinal parasites in this tropical region according to their percentage

MATERIAL

This article is organized on the basis of the results of stool examinations of two thousand five hundred patients from all social classes made during four years in Laboratorio Carlos Chagas in the city of Belo Horizonte, Brazil

METHODS

In nearly all the patients an examination was also made after concentration of cysts and eggs For this the Hoffmann, Pons and Janer's sedimentation method

TABLE I

PROTOZOA	Infected Patients	Percentage
<i>Endamoeba histolytica</i>	259	10.3
<i>Endamoeba coli</i>	621	24.8
<i>Endolimax nana</i>	58	2.3
<i>Iodamoeba bütschlii</i>	11	0.4
<i>Giardia intestinalis</i>	251	10.0
<i>Chilomastix mesnili</i>	155	6.2
<i>Trichomonas hominis</i>	35	1.4
<i>Balantidium coli</i>	4	0.16

(4) was employed A few times, however, De Rivas's (5) and Faust and associates' (6) methods were used

RESULTS

Data of stool examination of two thousand five hundred patients are shown in Tables I and II

*From the University of Minas Gerais School of Medicine

CONCLUSIONS

The commonest protozoa found by stool examinations of two thousand five hundred patients were *E coli* (twenty-four and eight-tenths per cent), *E histolytica* (ten and four-tenths per cent), *G intestinalis* (ten per cent) and *C mesnili* (six and two-tenths per cent)

The most frequent helminths in the above two thousand five hundred patients were *T trichiura*

TABLE II

METAZOA	Infected Patients	Percentage
<i>Ascaris lumbricoides</i>	489	19.5
<i>Necator americanus</i>	366	14.6
<i>Trichuris trichiura</i>	513	20.5
<i>Strongyloides stercoralis</i>	217	8.6
<i>Enterobius vermicularis</i>	73	2.9
<i>Taenia sp</i>	23	0.9
<i>Hymenolepis nana</i>	1	0.04
<i>Schistosoma mansoni</i>	100	4.0

(twenty and a half per cent), *A lumbricoides* (nineteen and a half per cent), *N americanus* (fourteen and six-tenths per cent), *S stercoralis* (eight and six-tenths per cent) and *S mansoni* (four per cent)

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Some Clinical Studies on the Psycho-Somatic Background of Peptic Ulcer*

By

ASHER WINKELSTEIN, M D

and

LEONARD ROTHSCHILD, M D

NEW YORK NEW YORK

INTRODUCTION

UP to recently peptic ulcer was considered a local, somatic disease. Irritating factors, excessive hydrochloric acid and increased peptic activity, acting on a mucosa constitutionally susceptible, was the conventional explanation for the mechanism of its production.

In recent years, dissatisfaction with this concept has arisen. There has been an increasing tendency to regard ulcer as the localized expression of a generalized constitutional disturbance and primarily as a disease of psychogenic origin. Together with certain other diseases peculiar to civilization, such as Grave's syndrome, cardiospasm, essential hypertension, mucous and indeterminate ulcerative colitis, peptic ulcer is generally regarded today as a "psycho-somatic" disease.

Alexander (1) has well stated "the relation of psychoanalysis to medicine cannot be restricted to its contributions to psychiatry. Psychic conflicts, especially unconscious tendencies, influence somatic processes and the study of psychogenic factors in somatic disorders is one of the important contributions of psychoanalysis to present day development."

As far back as 1914, Westphal (2) stated "Peptic ulcer must be divested of its appearance as an independent pathological entity. There is an etiological relationship between neurosis and ulcer." In a paper the previous year (3) he and Katsch had been even more emphatic "The existence of a neurosis (in the sense of unstable nervous equilibrium) is not evidence against the presence of a duodenal ulcer but proof that it exists. Duodenal ulcer is a single phenomenon in the great group of gastric neuroses. The etiology is vegetative and nervous. And it is the persistence of the neurosis which independent of the anatomical lesion prevents a state of quiescence or equilibrium in the vegetative nervous system."

Probably because of the war these papers excited little interest and the treatment of duodenal ulcer continued, in the words of Von Bergmann (4) "hardly better than those dermatologists who treat the skin alone and try to heal the lesion with washes, salves and dressings. Our therapy is merely indulgence of the mucosa, protection from damage and relaxation of the muscle. Until some sort of therapy arrives which will deal with the abnormal reaction of both organ and organism, half a stomach will still have to be removed to eradicate a lesion the size of a lentil on either side of the pylorus. It remains our best therapy but that is only because our 'dermatology' fails us."

In 1931 the theme reappears and begins to attain volume. Russ (5) states it in this way "The ulcer-bearing individual belongs to a distinct type and from birth is predisposed to the development of chronic ulcer. This type is the high strung, emotional, so-called vagotonic individual with sensitive nervous system. Experience seems to show that there is a tendency to the formation of ulcer in certain individuals and no matter what treatment is undertaken, recurrence is almost certain to take place. Ulcer patients are made worse by influences operating through the nervous system. They are cured, if ever, by treatment that is successful in relieving them from emotional strain. Experience and common sense both seem to point to the conclusion that the mystery connected with the origin and behavior of chronic peptic ulcer is in some way connected with the patient's physical make-up and nervous organization."

Cushing (6) expresses himself as follows "All clinicians are familiar with these facts (1) highly strung persons are susceptible to nervous indigestion and associated ulcer, (2) ulcers become symptomatically quiescent and tend to heal when patients are put mentally and physically to rest (3) Symptoms are prone to recur as soon as the victim of the disorder resumes his former tasks and responsibilities, (4) it is only in man that ulcers occur spontaneously with any considerable frequency, (5) no satisfactory and all embracing explanation of acute or chronic ulceration of stomach and duodenum has been found, (6) physicians and surgeons differ widely in their views regarding the proper regimen to follow in its active stage and how to forestall its tendency to recur when once healed and even those surgeons who believe that most ulcers should be operated on differ in the procedures which they advocate for its cure or alleviation."

Dunbar (7) says, "We are emerging from a period of parallelism which might be designated a period of 'either or' and becoming interested in psychosomatic interrelation. In the sequence of events which precede actual tissue changes in the old sense, when the organism loses its power over its parts or the parts become recalcitrant we have disease ranging from physiological to structural alteration. There is no such thing as a purely psychic illness or a purely physical one but only a living event taking place in a living organism alive only by virtue of the union between psyche and soma."

In therapy we try to distinguish between the injurious agent and the mechanism. We are coming to realize that the same must be done if the injurious

*From the Gastro-Intestinal Clinic of the Medical Department, The Mount Sinai Hospital, New York City.

agent is an emotion. Emotions cause visceral changes, which at first are reversible. But persisting pathological functioning tends to produce structural changes. We are familiar with fear, hunger, rage, etc., as responses of the organism involving secretory and contractile mechanisms."

This study was undertaken to answer a simple question. Given a series of ulcer patients of suitable age and intelligence is it possible to determine from an ordinary psychiatric interview the existence of psychic conflicts of such a degree as to warrant the assumption that these have some etiological significance to the ulcer syndrome.

There were admittedly some disadvantages. These patients had been attending the Gastro-Intestinal Clinic and were being treated only along organic lines. The psychological approach was new to them, and therefore, some of the patients were resistant to the examination.

Nevertheless, the case histories obtained from 33 young adult males with duodenal ulcer serve to show characteristic psychic backgrounds. Limitation of space will not permit of the presentation here of all of these cases. However, a few strikingly illustrative case histories will be given briefly. The psychiatric interviews were carried out by one of the authors (L. R.).

Case 1. Mr. G., age 23. Duodenal ulcer. Anxiety dreams for period of gastric symptoms—two years. Fighting with guns, knives, fists. Awakens before he is shot, with terror. No conscious anxiety. Excitable, irritable, loses temper quickly. Head feels funny when he gets mad grinds teeth. Feels like fighting right away but never fights—does not know why himself. Perhaps somebody is better than he is. Very much afraid of being beaten up.

Wife is frigid. Intercourse is distasteful to her—has to force it on her—"that's why I get nervous." There is a quarrel every time. Never has struck her but every time he gets angry does not know what he will do. Afraid he may do something violent that will send him to jail. Murder?

(From wife) "The minute I open my mouth, he kicks. Moans in his sleep, sometimes all night. One minute he is so good you can eat out of his hand, the next there is no holding him. Hollers for a while and then goes out of the house and stays away for a couple of hours." Wife does not know what he does. Patient has changed markedly for the worse since he has been married. Patient's sisters have made a lot of trouble between him and his parents over money.

Case 4. Mr. S., age 53. Penetrating gastric ulcer. Old luetic (1911). Arterio-sclerosis. In hospital 1932 where gastric ulcer was diagnosed. Painter, but never any symptoms of plumbism. Patient has been nervous all his life. First definitely evident at age of twenty when he was in the Russian Army at the time of the Russo-Japanese War. Was a socialist, against the government, did not want to fight. Very much afraid of death. Finally deserted across the Austrian border. Then had cold sweats and shivers of fear lest he be discovered, returned to Russia and shot. Since then he has been more nervous.

For many years used to awaken at night in terror from dreams of being back in Russia and captured and ready to be shot. In U. S. economic conditions were bad. Had a lot of mistreatment which he resented. This always brought on nervousness. Never a fighting person. If someone took advantage of him or was dishonest to him, he couldn't take it with a smile, would shiver and shake, become emotional and abuse the person as much as possible. Never has fought in his life. Does not know why. "When it comes to fist, I get calm and keep away." For years past has felt this emotional reaction in his stomach. Never saw

mother again. Missed her as long as she was alive. Very much attached to her. Was her favorite child. Dreamt of her frequently and still does at fifty-three. Father died suddenly. When patient received the news he cried for two days (age 48). Liked father very much better.

Married at thirty-three. Wife frigid. Patient passionate. Coitus interruptus for first ten years. In quarrels with wife patient has same shivering and shaking, emotional tenseness centering in the stomach that he had thirty years ago. Definite loss of libido in past two to three years since present illness became acute. Last few years he has had major episodes of nervousness only when he comes across what seems to him an injustice—such as from the boss on the job. When he gets mistreated, he gets aggravated, then goes up in the air and then his mind escapes from ego control. Patient shouts and yells. Then his body feels hot or cold, his arms and legs shiver and shake, his stomach pains begin. This may last a couple of hours but usually the stomach pain remains a day or so after the nervousness has gone.

Case 17. Mr. W., age 59. Duodenal ulcer. This patient has been operated on five times. Present illness began in 1914 when patient was forty-two. Six months later had a gastro-enterostomy at Mount Sinai Hospital (Dr. Berg). For twenty-two months he was worse off, then the Murphy button was removed at Fordham Hospital. After that was better for a year. Then a third operation disconnecting the gastro-enterostomy at Flower Hospital (also by Dr. Berg). Three years later became sick again. At the fourth operation another gastro-enterostomy was performed at Mount Sinai Hospital by Dr. Berg. Fifth operation consisted in a partial gastrectomy in 1924 at Mount Sinai Hospital. Then he was well for six years. In 1930 was in Mount Sinai again but no operation was performed. From 1930 to 1934 came to the follow-up clinic, was told he needed operation again but he couldn't stand it because he was too weak. In 1934 was on ward again, first on surgical then on medical wards.

Patient has never been clinically nervous. He is not quick tempered or excitable. Easy going. He is a man of peace and does everything to escape from fighting. Even if he was struck he would not fight back. When faced with the necessity of combat, his "insides get scared," heart beats fast, skin becomes pale. In moments of danger, patient gets mixed up, forgets where he is. For instance, if he hears a fire alarm, wants to run away. Does not know what he is afraid of but something irresistible impels him to run away from danger. Patient awakens many times at night with the fear that the house which is not fire proof, is on fire and has to go to the door or window to reassure himself. Very often he is afraid to fall asleep for this reason. Has the fear of being run over on the street. Always wants to cross until the light is in his favor and even then "shivers and shakes" until he is on the other side (never has been in any real peril). Patient is not afraid of operations or death, but can't stand pain or the sight of blood.

Patient's wife has a hot temper. Things have to be just so and if not she goes right up in the air. At first after marriage he tried to fight back and assert himself but soon found it was no use and gave up the struggle as useless. Then everything had to be in its proper place and every corner had to be spotlessly clean. Patient did not dare move the slightest object out of position. If he did he would have to put it back. Had no authority whatever in the house while she was there. Was never able to do anything to her satisfaction. Was either too slow or too inefficient. So finally gave it up as a bad job and let her do it all. Even before when patient was well his wife was not satisfied with his earnings and went to work. When he was sick she took over the task of making a living altogether. She would get more and more disgusted with him and his pains. Very often at night his aches and pains would annoy her so that she couldn't sleep. So finally for

sixteen years they have had separate rooms. Long before that every time there was a domestic squabble, she wouldn't let patient approach her sexually so patient gave that up also.

Patient stays at home and reads a paper and is OK. He goes out and gets frightened and right away the pains begin. He has even noticed that he awakens from anxiety dreams, such as being held up and robbed, with the characteristic pains. Patient ends the interview by saying, "I wish you would speak also to my wife."

Case 28. M. R., age 26. Duodenal ulcer. Father died ten years ago. Patient oldest of five sons—had to be head of the household. His brothers objected and there was friction that has continued to the present day. Mother has always been the nervous, worrying type. Each day there would be something else patient had to listen to about what this boy or that was doing. "Why can't you be like that?" Mother consistently inconsistent, there would be a quarrel each day, patient would argue with her day and night and get nowhere. Patient has always had arguments with mother and brothers. He thinks more clearly and further ahead. They never agree with him. This leaves a chronic bad feeling. Patient's temper is inhibited. Feels he can't let temper go. "What's the use—my own family?" When he can't let self go, feels it in his stomach. Tenses it up. Feels sore in body and mind.

For years patient has been hoping and planning to get family away from lower east side. It has been talked about for years. Four months ago he brought enough pressure to bear to take the decisive step. But he had to do it all himself, buy the furniture, sign the lease, etc. As soon as the family moved, everybody found fault with everything. It was his fault, things were better where they had been, etc. It was chiefly his mother who didn't want to leave the east side and who influenced the other sons. She is the chief dissatisfied one now and loses no opportunity to throw things up to the patient. It is always, "Well, you signed the lease and it's your fault." Patient gets no pleasure out of his home. It represents the frustration of his dearest wish.

Gastro-intestinal symptoms set in two months ago and two months after above situation became acute.

DISCUSSION

None of the thirty-three individuals interviewed seem to be free from internal strife. And it seems to be of a typical kind. Whether the struggle is with the environment or an object, an impersonal fate or an unloved helpmate, it seems nothing can be done about it save to bear it to the best of one's ability. There is nothing available in the way of a rough and ready solution. It is a subacute or a chronic conflict of a similar category to those seen in the usual psychoneurosis involving potent forces within the mind itself. Perhaps a series of thirty-three normals would show internal tension along similar lines. But it is much more likely that the repressed energy would get out in some fashion or other in the form of action or explosion. Also, it is much more probable that normal individuals are in such states of inward tension only occasionally. These ulcer patients, however, are suffering from chronic frustration and inward direction of strong emotional stimuli. It is apparently the chronic state which is harmful.

These people just don't seem able to get outwardly angry. When they are angry they feel it "inside." It "grips" them within. Consciously more often than not this increase in psychic tension is connected with the onset of the stomach pains.

It would seem that the content of the repressed energy is strongly sadistic and that it is the tabooed aggression and violence that is forced to take this

visceral pathway. This is a familiar pattern in psychoanalytic thinking. Freud has postulated from his studies a "Destruktionstrieb." For psychic syndromes are known in which the organism tries with all its power at its command to bring about its own injury. Such are the self-imposed torments of the compulsive or the suicide of the depressed. When the sadistic drive is freed from whatever unconscious bond or amalgam that contains it and finds no available pathway leading to the object, it is inevitably turned against the ego. It is suggested that duodenal ulcer is one of the many ways in which this sado-masochistic conflict works itself out. It is not suggested that this is the only available pattern, to say nothing of the possible psychic ones, but it is suggested that possibly this particular type of conflict is specific for ulcer patients.

Eli Moschowitz in his discussion of the psychogenic origin of organic diseases (8) states, "The psyche of patients with peptic ulcer is uniform. They are inimitable, sensitive, self-absorbed and mentally inelastic. They are aggressive but often swallow their anger." After a consideration of the neurogenic theories, he concludes, "It seems permissible to argue that both the cause and mechanism of ulcer are mediated through nervous pathways."

The problem now veers to the mechanism whereby psychogenic factors influence the somatic expression. Cushing (6) has presented experimental evidence that a parasympathetic center exists in the diencephalon. He regarded peptic ulcer as the result of a disharmony between the two divisions of the vegetative nervous system resulting in spasm and vascularity. Cushing's observations received support from Beattie (9) who produced small patches of hyperaemic gastric mucosa after a half-hour's stimulation of this center. This effect was abolished by sectioning the vagi. Light, Bishop and Kendall (10) by introducing small doses of pilocarpin into the cerebrospinal fluid produced the same gastric disease as large doses subcutaneously, namely, local gastric patches of anemia associated with the rupture of minute surface capillaries and prolonged contraction of the blood vessels resulting in areas of devitalized cells susceptible to digestion by gastric juices resulting in necrosis and liquefaction. This is not due to increased acidity but to spasms of blood vessels and muscularis under the influence of central nervous stimulation.

Cushing (6) has taken the venturesome leap from the psychic to somatic. He states "Those favorably disposed toward the neurogenic conception of ulcer have in process of time gradually shifted the burden of responsibility from the peripheral vagus to its center in the medulla, to the midbrain and now to the interbrain, newly recognized as a highly important station for vegetative impulses easily affected by psychic influences. So it may easily be seen that highly strung persons through emotion or repressed emotion incidental to continued worry or anxiety or heavy responsibility are particularly prone to have chronic digestive disturbances and the hyperacidity often leading to ulcer—effects wholly comparable to those produced by experimental lesions."

Light and his co-workers (10) go further and say "The basic importance of the diencephalic regions in governing the vegetative functions has long been

known as well as the organic responses to emotional states of psychic origin. Apparently these centers under stimulation can so weaken the gastric structure that it becomes susceptible to digestion by its own juices. Thus an explanation is offered of acute gastric ulcer as a constitutional disease in which the origin and recurrence of symptoms is definitely linked with psychic disturbances."

In general, it seems fair to state, despite these observations, that the mechanism of peptic ulcer production through psychic pathways, still awaits elucidation.

SUMMARY AND CONCLUSIONS

A psychiatric examination of 33 young adult males with duodenal or gastric ulcer has been carried out. Space permits only the presentation of 4 illustrative cases in detail. The entire group revealed characteristic psychic backgrounds. These patients are suffering from chronic frustration and inward direction of re-

pressed, strong emotional stimuli with strong masochistic and sadistic tendencies. This chronic state of inward tension or drive bears a close relation to the incidence and recurrence of peptic ulcer. While much further work is necessary before one can draw a final conclusion, nevertheless, a review of the observations of others plus our own experience impresses one with the strong probability that peptic ulcer is a psychosomatic disease.

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The Nervous Stomach

By

O S JONES, M.D.
ST LOUIS MISSOURI

POSSIBLY the majority of patients complaining of their stomachs are suffering from a functional rather than an organic disease. Fullness and upper abdominal distress after meals, belching and failure to obtain relief from alkalis suggest a diagnosis of "gastric neurosis" especially when these symptoms are associated with nervousness, constipation, insomnia and loss of energy. We must carefully rule out gastritis, peptic ulcer, duodenitis, cholecystitis, cancer, appendicitis, and such general conditions as anemia, leukemia, hepatic cirrhosis and circulatory failure. Food-relief and soda-relief are highly suggestive of ulcer and such cases must submit to radiological examination. It is questionable if gastritis can be diagnosed without gastroscopy.

The author is slow to make a diagnosis of cholecystitis and restricts cholecystectomy to those cases in which stone is present. At the Marine Medical Clinic only one-tenth of one per cent of all admissions have been subjected to cholecystectomy.

Gastric cancer may be elusive in its early stages and X-ray examination should be insisted upon in all cases over forty years of age, who complain of stomach distress.

Gastric neurosis may be the only form of neurosis which the patient presents. Failure to receive help from other physicians often makes him a difficult patient to handle. A carefully taken history and a sympathetic discussion of his affairs may reveal that he is intensely worried, or overworked or the victim of some social injustice, or a perfectly frustrated person. Finances and in-laws are, in my experience, more common causes of worry than elaborate Freudian complexes of any sort.

Fluoroscopically, the stomach may be seen to be

subject to more or less intense spasm, not only at the pylorus but throughout the entire organ. The "spool" type of spasm is not infrequent, especially in thin women. In a few cases, where extreme pain is present, the stomach silhouette may be almost obliterated temporarily by a massive gastric spasm. The tone of the organ usually is good and atonic stomachs associated with pain are rare. The resemblance of spastic stomach to spastic colon is obvious, and the two may co-exist, but the latter may be assumed to cause lower rather than upper abdominal distress.

Chronic appendicitis (if there is such an entity) may best be recognized by its acute or subacute exacerbations, exhibiting the classical features, and these signs are of greater value in diagnosis than roentgenological studies.

Once organic disease has been confidently ruled out and a diagnosis of nervous stomach has been made, the patient himself must be sympathetically understood and treatment directed to the entire socio-psychological elements in his particular case. In this valuable work, good sense and encouragement are in ordinary cases, more needed than technical psychoanalysis. If a diet is prescribed, one should avoid too great restriction. Temporary limitation of starches and roughage may be of value. In adipose individuals, caloric intake needs to be lessened and a regimen outlined for weight reduction. In ptotic individuals the familiar "long thins" added nourishment is needed. When constipation is present, a daily saline enema is not only harmless but helpful and produces a good reflex effect on the stomach. If achilia is present, dilute hydrochloric acid, in water or in milk, with or following meals, may be used. However, the medicinal mainstay of treatment of these nervous stomachs is

sedative and belladonna. A favorite prescription of the author is as follows:

R phenobarbital gr $\frac{1}{2}$
Atropine sulphate gr 1.200
Misee fiat cap Sig — one after each meal

Finally, any of the bulk-producing laxatives may be tried if necessary.

The diagnosis of "nervous stomach" should depend upon a highly scientific elimination of organic disease in the upper abdomen. The treatment, however, is an art rather than a science and success is dependent, largely, on understanding the mental problems of the individual, and one's power of mental suggestion and encouragement.

Insulin Reaction and the Cerebral Damage that may Occur in Diabetes*

By

FRANCIS D. MURPHY, M.D.

and

JAMES PURTELL, M.D.

MILWAUKEE, WISCONSIN

INSULIN, when first introduced, was used with caution and the dangers of hypoglycemia from overdosage were emphasized. The advent of Sakel's insulin shock therapy in the psychiatric states has resulted in voluminous literature on hypoglycemia. Much of this deals with the therapy of the various psychoses. The significance of insulin reaction was minimized, and the safeguards which had been so effective were somewhat slighted. There is, however, increasing study of the mechanism of insulin reaction and the possible pathologic changes particularly with reference to the central nervous system, which may result from prolonged hypoglycemia. And there has been recent re-emphasis upon the catastrophic end result of severe insulin hypoglycemia in diabetic patients. The case reported here is an example of this danger.

REPORT OF CASE

S. S. Hospital Number 280182, white female, 13 years old. The patient, a thirteen year-old white school girl was admitted to the Milwaukee County General Hospital at 9:00 a. m. on March 8, 1941, in coma.

The *past history* revealed that the patient had had all the usual childhood diseases. At the age of four she had been under observation for six months for tuberculosis, but was discharged as non-infected. At the age of eight she was struck by an automobile, incurring a cerebral concussion which left her unconscious for 24 hours. There were no apparent residual injuries from this accident.

Her educational development had been normal. Prior to admission she was in the seventh grade, and had maintained an excellent scholastic record. There were no obvious personality defects.

The *family history* was negative except for the presence of diabetes in a paternal uncle.

The *present illness* began one month prior to admission, when she developed diabetes. The symptoms culminated in diabetic coma, and she had been hospitalized and treated for this complication in another institution from February 11 to February 17, 1941. Upon release her diabetes was controlled on diet and Protamine Zinc Insulin, 15 units in the morning and 15 units at night. This dosage was later increased to 25-0-25. For two days prior to admission the child complained of continual hunger.

On March 8, the morning of admission, she awoke about 4:30 a. m. sweating, nervous, and confused. Her mother, upon the advice of her family physician, gave her the

regular dose of protamine insulin (25 units) at this time. At 6:30 a. m. she no longer responded. She was incontinent, tossing about and screaming, and there were choreiform movements of the face and extremities. Shortly after this, there was an involuntary micturition and defecation. She then developed violent convulsions and was restrained in bed with difficulty. It was in this state that she entered the hospital—four and one-half hours after the onset of the hypoglycemic reaction.

Entrance examination revealed a tall, thin, pallid girl of 13 years. She was comatose. There were restless choreiform and athetoid movements of the face and extremities. The arms and legs were quite spastic. The temperature was 101.0° F., pulse 104°, respirations 20, and blood pressure 130/70.

The pupils were equal, dilated, and reacted to light. There were incoordinate movements of the eyes. The fundi were normal. No abnormalities were found upon examination of the ears, nose, mouth or neck. There was a soft systolic murmur at the pulmonic area of the heart. The lungs, abdomen and external genitalia were negative. The extremities were spastic.

Urinalysis was negative for sugar, acetone, and diacetic acid. The diagnosis of hypoglycemic shock was made, and therapy instituted immediately. Twenty-five cc. of 50 per cent glucose were given after completion of the admission examination, and an additional 40 cc. of 50 per cent glucose were administered within the ensuing forty-five minutes. The active convulsive movements ceased after the second dose, but the patient remained comatose, and there were still irregular athetoid movements of the extremities.

The further therapy instituted, and the follow-up studies of the blood and urine sugars are summarized in Table I. It will be noted that the initial blood sugar value, taken after the administration of 45 gm. of glucose, was only 96 mgm. per cent. On the second hospital day it was over 200 mgm. per cent, and thereafter was maintained at near normal levels. The carbon-dioxide combining power of the blood remained within normal limits throughout. Sugar re-appeared in the urine on the second day and remained intermittently until the sixth day, when the patient was stabilized on insulin and diet.

Despite the adequate control of the initial hypoglycemia and the regulation of the diabetes, however, the patient failed to respond. She remained comatose until the fourth hospital day, when she reacted to verbal orders and called for her mother. There was no other attempt at speech.

On the fifth and sixth day the patient recognized members of her family, responded to simple commands, and was able to take a liquid diet. However, she was emotion-

*From the Department of Medicine, Marquette University Medical School and the Medical Clinics, Milwaukee County Hospital, Milwaukee, Wis.

ally unstable, laughing or crying purposelessly, and her speech was limited to "yes" and "no." She was incontinent of urine and feces.

Frequent physical examinations during the period of coma revealed slight neck rigidity, diminution of all deep reflexes, absent abdominal reflexes, bilaterally positive Babinski's, positive Brudzinski (contralateral reflex) on the right, there was no clonus or increased spasticity. On the fifth day, however, she developed a flaccid paralysis of the facial muscles and the extremities on the right side. This disappeared the next day.

The temperature remained elevated until the sixth hospital day, reaching a maximum of 103.8° rectally on the fourth. The laboratory data is summarized in Table II.

From the sixth day until her discharge from the hospi-

tal, there was little change in the mental condition of the patient. She was aware of her environment and now said, "Mother," "Thank you," "Yes," and "No," but was unable to voice connected thought. On attempting to write her name, she succeeded in spelling the first four letters, and this in child like block print. There was no evidence of motor paralysis. The diabetes was now controlled on diet and 30 units of protamine insulin.

On March 29, fifteen days after admission, she left the hospital on release.

On April 3, two weeks after discharge, there was little advance in her mental status. Her mother reported that she had made a laborious adjustment to home life and was only then becoming accustomed to the other members of her family. Her actions were those of a docile child follow-

TABLE I

Hour	Sugar	Urine Acetone	Diac.	Blood Sugar	Van Slyke	Insulin	Fluids
First Hospital Day							
Adm	0	0	0				65 cc. 50% glucose IV
3 30	++++	0	0			0.2 cc Adrenalin	25 cc 50% glucose IV
4 30				96 mgm %			
5 10							500 cc. 10% glucose IV 1000 cc N saline subq
8 30							30 cc 50% glucose orally 1000 cc. 10% glucose IV Total 210 gm glucose 220 cc fluids
Second Hospital Day							
5 00	++++	0	0	237 mgm %	40		
8 00	++++	tr					1000 cc N saline subq
1 30	++++	tr	0	234 mgm %	38	Reg 25	
4 30	++++	++				Reg 25	1000 cc N saline subq 200 cc. dist. HOH 80 cc. Na lactate
9 00	0	0	0				50 cc. 50% glucose IV Total 25 gm glucose 220 cc fluids
Third Hospital Day							
5 00	tr	0	0	143 mgm %	33.4		1000 cc N saline subq
10 00	0	0	0				
12N	+++	+++	0	169.5 mgm %	36.8		400 cc distilled HOH 80 cc. Na lactate
4 00	+++	+++		179.8 mgm %	39	Reg 10	
6 00	++++	+++	++			Reg 10	
9 00	0	++	++				600 dist. HOH 80 cc. Na lactate 500 cc. N saline Total No glucose 2600 cc fluids
Fourth Hospital Day							
5 00	0	++++	++++	100 mgm %	47.1		400 cc dist. HOH 80 cc Na lactate
8 00	0	+++	++			Reg 5	1000 cc. N saline
9 00	+++	++	++			Reg 5	
11 00	+	++++	++++			Reg 25	1000 5% glucose IV
12N	+	++	tr				
3 00	0	tr	tr				
4 00	0	0	0	80 mgm %	45.1		1000 N saline
6 00	0	0	0				400 cc. dist. HOH 80 cc Na lactate
10 00	0	+++	++				
12 00	+	++++	++++				Total 50 gm glucose 3400 cc. fluids
Fifth Hospital Day							
5 00	++++	+++	+++	117 mgm %		Reg 5	
7 00	+	++++	++			Reg 25	1000 cc. 5% glucose IV
9 00	++	0	0				500 cc. N saline
12N	0	++	++				
3 00	0	++++	+++			Reg 15	25 gm. glucose orally
5 00	++++	++				Reg 25	1000 5% glucose IV
7 00	0	0	0				Total 75 gm glucose 2400 cc. fluids
10 00	0	0	0				
Sixth Hospital Day							
5 00	0	0	0			Reg 15	Started liquid diet
12N	0	0	0			Reg 15	
6 00	0	0	0			Reg 15	

ing simple acts when clearly demonstrated to her. She was still inarticulate, although she was now repeating simple phrases and could count to twenty. Her mother was attempting to teach her to write.

The subsequent course of this patient was very unsatisfactory, as far as the mental condition was concerned, and had not changed in the past year. The aphasia persisted, though with special teaching, she was able to take up first grade reading. The mother refused to have her daughter subjected to psychiatric testing.

The next and last report which we obtained was that on June 13, 1942, the patient developed diabetic coma and died at another hospital. No permission for autopsy was granted.

Summary of Case. A thirteen-year-old white female diabetic patient treated with protamine zinc insulin

TABLE II
Laboratory data

Blood Counts	37	38	311	
Hemoglobin	14.5 gm	13.5 gm	11.7 gm	
Red cells (million)			3.96	
White cells	16,000	17,400	7,150	
Differential (percentages)				
Segmented forms	90	79	62	
Band forms	2	4	3	
Lymphocytes	6	12	31	
Monocytes	2	7	9	
Eosinophiles	0	0	1	
Basophiles	0	0	0	
Wasserman and Kline (blood and spinal fluid) negative				
X-rays of chest and skull negative				
Spinal Fluid Studies	37	38	39	312
Red cells	16	0	12	435
White cells	3	16	50	17
Protein	50.0 mgm %	35.2 mgm %		
Sugar	150.0 mgm %	131.0 mgm %		
Chlorides	700.0 mgm %	760.0 mgm %		
Pressure (mm. water)	42.0	250.0	250.0	100.0

potential dangers of insulin shock therapy in the treatment of the psychoses, and the use of this therapy has provided the opportunity for careful neurological and psychiatric study of the effects of hypoglycemia.

The hypoglycemic state, whether spontaneous or induced, is characterized by bizarre and varied symptoms. In general, it is manifest in three stages. The first, a prodromal period of ten to thirty minutes, is characterized by lassitude, mental confusion, irritability, and restlessness. This is followed by profuse perspiration increasing confusion and restlessness, and at times, convulsions. This stage proceeds to stupor and coma, or in other cases, to increasing excitement, agitation, somnambulism, delirium, or fugue states. The third, and final state is that of deep coma, usually with convulsive phenomena of variable type, disturbances in reflexes, nystagmoid movements, and frequently motor palsies. The period of coma particularly is manifest by bizarre motor disturbances, athetoid movements of the extremities, grimacing of the face, sucking movements of the lips, clonus of the jaws and clonic movements of the eyelids and extremities. An attitude of decerebrate rigidity, with extension, bilateral adduction and inward rotation of the arms, clenched fingers, and open, staring eyes may develop.

In many cases disturbances of consciousness without the advent of coma or the motor phenomena were the outstanding symptoms. These included catatonia, delirium, irritability, tinitus, amnesia, negativism, automatism, hallucinations, hysteria, and partial or complete unconsciousness. At least two cases of psychosis associated with hypoglycemia have been reported (Anderson (8) and Witten (9)).

Several classifications of the syndrome have been offered (10, 11, 12, 13). In general, these are based upon the area of brain involved. That of Wilder (12) is perhaps the most comprehensive. He groups the symptoms under the following sub-heads: I Vegetative-vasomotor; II Cardiovascular; III Bulbospontine; IV Corticospinal; V Striothalamic; VI Cortical. A similar grouping is made by Ingham et al (13). Their conclusion is that the site of greatest disturbance is in the region of the basal ganglia, central gray matter, and the brain stem.

While the hypoglycemic syndrome, with its potential aftermath of cerebral damage, has not been extensively publicized in connection with studies of diabetes, a number of case reports have appeared. Twenty-six cases, by various authors (2, 8, 9, 14, 15, 16, 17, 18, 19, 20, 21, 22) are reviewed in this report.

In these cases the most common aftermath of cerebral damage is profound mental and personality change. The most extensive reaction may leave the individual at the intellectual level of idiocy, with all signs of rational thinking, higher feelings, and reasoned action absent. In other instances there is a variable degree of mental retardation, with apathy and dullness. At times these changes progress to true psychoses requiring institutionalization. A post-hypoglycemic syndrome resembling Parkinsonism has also been reported. Objective neurological changes are frequently observed during the hypoglycemic shock, and not uncommonly persist for months following emergence from it. Aphasias are probably the most frequent of these. Persistent hemiplegias have also been reported.

went into hypoglycemic shock, and remained in it for four days, although the blood sugar levels had returned to normal 12 hours after she entered the hospital. After emerging from the coma there was evidence of residual cerebral damage.

DISCUSSION

The clinical features of this case are similar to those reported by others who have pointed out the potential toxicity of insulin.

Joslin (1) as early as 1922 referred to a fatal case of hypoglycemia in a diabetic taking insulin. Other cases of fatal hypoglycemia have been recorded since, and pathological studies of the changes in the brain have been published by Baker and his associates (2), Pemberton (3), Terplan (4), Lindsay et al (5), Saks and Alexander (6) and Wohwill (7).

There has been increasing emphasis recently on the

Table III summarizes the cases reviewed. The end results cited in this chart are those which were particularly prominent, they do not necessarily include all the changes resulting from the insulin reaction. The number of cases scarcely permits generalization as to the incidence or the factors influencing this type of insulin shock. It will be noted, however, that males outnumber females (eighteen to six) and that a relatively large number of reactions occurred in individuals under the age of thirty. The duration of the shock symptoms apparently had little effect on the end result, although the majority of deaths occurred within 24 hours. Nine cases reported the use of protamine zinc insulin, eleven, regular insulin, and in six the type was not mentioned. No reference has been made to the size of dose used because reports in this respect were incomplete. It might be mentioned, however, that one individual survived a dose of 490 units of protamine zinc insulin, taken in an attempt at suicide, without apparent residual damage (22).

Pathology The first pathological study of the effects of hypoglycemia in diabetics was reported by Wohwill (7) in 1929. He reviewed the cases of two patients who had died in insulin shock. There were uniform

primary nerve cell injuries, swelling of the axis cylinders, and moderate glial proliferation found on autopsy of the brain. In 1932 Terplan (4) reported the case of a 16 year-old diabetic who received an overdose of insulin, developed convulsions, coma, and expired after three days. At autopsy there was marked edema of the brain, and extensive colliquation of the ganglion cells, most pronounced in the third cortical layer. There were some degenerative changes of the glial tissue.

Since these early reports, there has been a considerable study of the cerebral changes both in diabetics and in patients given insulin shock therapy. Post-mortem studies have been included in the works of Baker and his collaborators (2), Malamud and Grosch (23), Weil et al (24), Pemberton (3), Saks and Alexander (6) and Lindsay et al (5).

No changes characteristic of hypoglycemia have been described. There is ample evidence, however, of widespread damage, and of changes which, in the event of survival, are irreversible. Multiple petechial hemorrhage, or more extensive hemorrhage with localized areas of encephal-melacia and cyst formation are frequent findings. Irregular dilatation of the vascular

TABLE III
Summary of cases reviewed

No	Author Ref No	Sex	Age	Duration of Diabetes	Type of Insulin	Duration of Shock Symptoms	End Result
1	2	M	39	20 years	Unknown	Hours	Death
2	2	M	65	Unknown	Regular	In coma thrown into shock	Hemiplegia
3	2	M	8	1 year	Protamine	7 days	Mental retardation
4	2	F	15	11 years	Protamine	7 days	Aphasia right paresis mental retardation
5	2	F	21	17 years	Regular	7 days	Personality changes
6	2	M	49	14 years	Regular	62 hours	Death
7	2	M	53	4 years	Regular	5 hours	Death
8	2	M	64	3 years	Protamine	8 days	Death
9	2	M	39	7 years	Regular	10 days	Mental changes
10	3	M	30	2 years	Regular	4 hours	Death
11	4	M	16	Unknown	Regular	3 days	Death
12	6	F	44	6 years	Protamine	8 days	Death
13	6	M	55	7 years	Protamine	24 hours	Death
14	8	M	13	Unknown	Unknown	4 days	Mental deficiencies
15	9	M	48	4 years	Regular	? (developed during treatment of coma)	Organic psychosis
16	14	M	22	2 years	Protamine	5 days	Imbecile
17	Cited 14	M	16	12 years	Unknown	Unknown	Mental apathy and dullness
18	15	F	23	7 years	Unknown	Unknown	Mental confusion
19	16		13	Unknown	Unknown	4 days	Mental deficiency
20	18	F	33	8 years	Regular?	9 days	Mental invalid
21	14	M	48	17 years	Regular	7 hours	Aphasia which cleared up
22	20		33	Unknown	Unknown	Unknown	Aphasic
23	22	M	27	5 years	Protamine	2 days	None apparent
24	22	F	46	7 years	Protamine	36 hours	None apparent
25	17	M	26	Unknown	Regular	3 days	Personality changes, Parkinsonism post-encephalitic type
26	8	M	7	2½ years	Protamine	Frequent continuous	Imbecility

tree, thrombosis and perivascular extravasation with distention of the perivascular spaces are common. Proliferation of the glial tissue—either diffuse or nodular—have been described. There is atrophy of the cortex, with fatty or patchy demyelination of the cells. The injury to nerve cells is usually disseminated widely.

Experimental work by Grayzel (25) on rabbits revealed hyperchromatic cells with corkcreek processes in mild cases, and necrobiosis with involvement of the pyramidal cells of the third and fifth layers in the more severe reactions.

Mechanism of Action. The nature of the action of insulin and of hypoglycemia on the central nervous system is not known, though various theories have been offered. Considerable investigative work has been done and is still being done on this problem. Saks and Alexander (6) have reviewed the recent literature in their paper.

Discussion in detail of the theories and the experimental work supporting them is beyond the scope of this work, but the factors which have been considered may be summarized in brief as follows: (1) Insulin per se, is toxic to the brain cells (26, 28). (2) Hypoglycemia is accompanied by changes in the electrolytic balance. This is suggested by the observation of Sherrill and MacKay (28) that fatal convulsions may follow the intravenous injection of glucose in the presence of hypoglycemia. Corwin (29) was unable to find any support for this postulate in a later experimental study. Freudenberg and his associates (30)

were unable to show any relationship between symptoms and the presence of acetone, diacetic acid, or the bisulfite binding bodies of the blood. (3) The brain cell suffers from carbohydrate deprivation and resulting anoxemia. It has been shown by Holmes (31) that the brain can oxidize only glucose or other available carbohydrate, and the carbohydrate store of the brain tissue is minimal. In the presence of induced hypoglycemia, the glucose stores are used up and the tissues suffer from resultant anoxemia (31, 32, 33, 34). Damashuk and Myerson (34) first demonstrated a relative anoxemia in dogs during hypoglycemia, and Gellhorn (35) has made extensive studies on the relationship between hypoglycemia and anoxia. The clinical and pathological effects of prolonged anoxemia are similar to those resulting from hypoglycemia and it is probable that the action of insulin on the brain is closely associated with the oxidation processes of the tissues.

SUMMARY

1 The clinical observations on a diabetic patient who suffered severe hypoglycemic shock which resulted in residual cerebral damage and death the following year are reported.

2 Similar cases reported in the recent literature are reviewed.

3 The dangers of irreversible mental changes following insulin shock are pointed out.

4 The symptomatology, pathology, and mechanism of insulin action in hypoglycemia are briefly discussed.

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Jejunal Diverticula

A Consideration of Clinical Symptomatology and Case Report*

By

ARIE C. VAN RAVENSWAAY, CAPT. M.C., A.U.S.

and

GEORGE WARREN WINN, M.D.

BOONVILLE, MISSOURI

JEJUNAL diverticula, although rather frequently discussed in the literature, still do not receive the attention from a diagnostic standpoint that they deserve. This is partly due to their rarity, partly because the majority of them never result in disease or produce symptoms, and chiefly perhaps because of the pleomorphism of symptomatology which is produced by the minority which are of clinical importance. In this respect they exhibit a contrast to Meckel's diverticula which are also quite rare but which, because of a fairly characteristic and generally recognized clinical picture, are usually considered in the differential diagnosis of pertinent cases.

The medical literature referring to jejunal diverticula was reviewed very carefully by Gerstle in 1938 (1). At that time he found 187 cases in the literature. This number has subsequently grown to approximately 228 (2, 3). The bulk of this group has been discovered at operation or autopsy. Johns (4) reviewing this phase of the subject in 1937 found that to that date only 26 cases had been discovered by X-ray examination, and of these only 17 had been confirmed by operation.

The true incidence of jejunal diverticula is difficult to arrive at. The percentage found at autopsy on inflation of the jejunum is higher than that found on X-ray examination. From the standpoint of clinical expectancy the latter figures are in some ways more significant. Case (5) in a series of 6847 gastro-intestinal examinations, found four patients with one or more jejunal diverticula, and in the same group found 85 cases of duodenal diverticula. Diverticula of the jejunum are frequently associated with diverticula of congenital anomalies elsewhere in the body (5). In approximately a third of the cases reported, multiple duodenal diverticula have been found.

The causative factors in these lesions have been considered by numerous authors. The review of Dixon et al (6) in 1938 covers the different theories advanced quite thoroughly. In separating known fact from assumption, it can be said that a portion of the lesions are congenital in origin as evidenced by their presence at times in very young infants (3, 7). It appears probable that others develop in the latter decades of life either on the basis of a congenital or an acquired weakness of the abdominal wall. "True" diverticula are said to have a muscle layer in their wall and "false" diverticula to be lined with mucosa and peritoneum only. However, when the sac becomes very large, the muscle layer, even if originally present, may become attenuated or even non-existent and in either event functionally impotent.

The point of origin as in the case to be reported is usually along the mesenteric border (8) and if a large amount of mesenteric fat is present and the lesion small and empty, it may prove difficult to find at operation. Rothschild reported that in 21 of 24 jejunal diverticula the lesion was so located along the mesenteric border.

A consideration of the symptomatology resulting from duodenal diverticula should be based upon the fact that the diverticular sac, while not a normal structure, in itself is not a cause of symptoms. The latter result from the varied complications which may occur. It is important to emphasize that complications occur in a minority of cases, and the demonstration of such a lesion in the presence of abdominal complaints is usually coincidental. The actual incrimination of a diverticulum should require the most careful consideration.

Certain physical characteristics of the sac contribute to the development of complications. Enlargement of the sac as well as relative enlargement in relation to the size of its neck, and the absence of an efficient muscular layer in its wall, all contribute to retention of contents with or without associated distention. The latter situations produce the most benign complications of clinical significance which occur. They may of course progress to the more serious situations to be described in subsequent paragraphs. The distress which ensues is a function of the "pain level" of the patient, the time involved in the cycle of filling and emptying of the sac, the degree of distention, and the relative amount of absorption from the sac. Some diverticula, as observed with the barium meal, fill promptly after the adjacent bowel is reached by the head of the barium meal and are visualized most clearly if only a small amount of barium is administered. This is indicative of an ample mouth, and if the sac is small it will probably be found to empty promptly. If the sac is large or dependent, it may be retentive for a variable period. Absorption may occur from such a sac but probably increased intradiverticular pressure or distention does not occur. A second type of sac fills comparatively slowly after the head of the barium meal reaches its level and may be missed entirely if only a small amount of barium is used. This type is usually discovered in serial films of the small intestine or in a routine five or six hour film after the barium meal. Its relatively slow rate of filling may be interpreted as indicating a poorly functioning stoma and, after filling, impaired emptying and distention may occur.

It may be postulated that absorption of retained

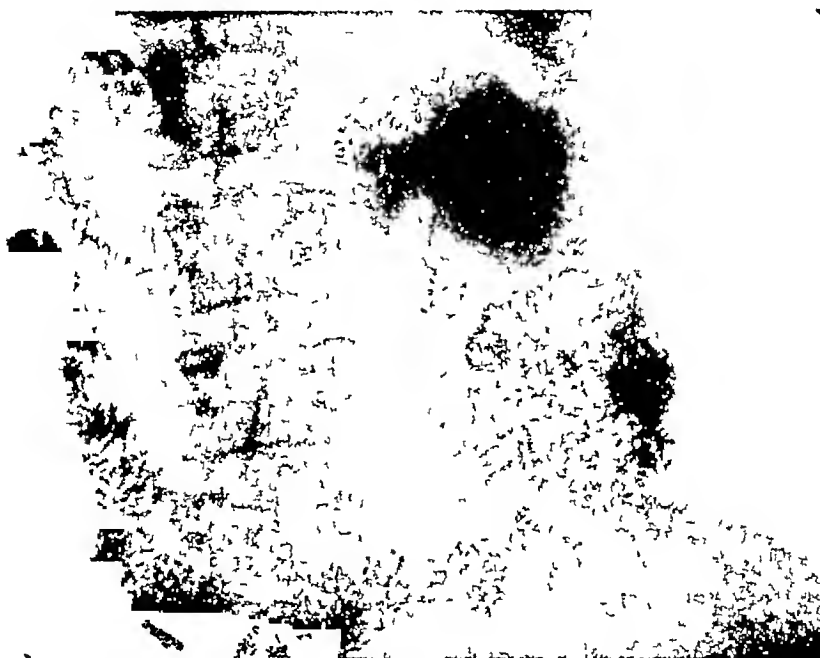
*From The van Ravenswaay Clinic.
Submitted October 26, 1942.

material which has undergone bacterial action may result in a mild diverticulitis, lymphangitis, or mesenteric lymphadenitis or a combination of them which results in localized tenderness with or without disturbances in the intestinal gradient. Symptoms from this cause should go and come in broad cycles covering periods of days or weeks or, if more severe, fluctuate in intensity over relatively long periods of time according to variations in the degree of retention and in the status of the retained material as affected by the diet, type of bacterial action available, and the general condition of the patient.

The symptoms resulting from distention in the sac are usually described as sensations of fullness, cramping, dull to acute pain, and localized tenderness. The pain of distention, when severe, has been described by Lockwood (10) as "bursting" in character. Its cycle of appearance and duration is a function of the filling and emptying characteristics of the sac. It usually ap-

pears in the upper intestinal segments resulting in nausea and vomiting. Acute jejunal diverticulitis is particularly prone to lead to gangrene and peritonitis. Perforation of a jejunal diverticulum, whether the result of infection and gangrene or of trauma, results in the spilling of small intestinal contents into the peritoneal cavity. In the absence of prompt surgical intervention a prompt fatal termination may be anticipated.

Other bizarre and frequently dramatic complications of jejunal diverticula are reported in the literature. The accompanying diagram indicates various mechanisms through which duodenal diverticula may cause trouble. The solid lines represent complications described in the literature and the dotted lines some which might reasonably be expected to occur. No instance of aberrant gastric mucosa was encountered as is frequently found associated with Meckel's diverticulum. An X-ray examination will usually not play a role in the diagnosis of these situations which,



Film showing stomach and small intestinal pattern one hour after the administration of barium by mouth. The diverticulum is visualized below the stomach.

pears from 30 minutes to several hours after meals. It may persist for a period of one to two hours, or a severe exacerbation may last for several days. Its relationship to meals is not so regular as that of classical peptic ulcer. In many reported cases, the symptoms have been continuous in nature and an attempt has been made to distinguish them from ulcer on this basis. However, in other cases as in that reported in this paper, there were remissions and exacerbations possibly resulting from self imposed dietary restriction subsequent to the appearance of symptoms.

Acute jejunal diverticulitis has been reported in several instances. The resultant picture is similar to acute appendicitis except that the localizing symptoms are ordinarily found in the left upper quadrant and paraumbilical region rather than in the right lower quadrant. It may be distinguished from the usual case of acute sigmoidal diverticulitis because of its higher location and greater likelihood for disturbances of the

because of their acute character, will usually lead to prompt surgical intervention. The possibility of jejunal diverticulum should be considered pre-operatively, however, in instances of unexplained hemorrhage, delayed motility of opaque foreign bodies, the presence of a clinical picture of perforated clinical viscus following non-penetrating trauma, and in unexplained sepsis associated with vague gastro-intestinal symptoms.

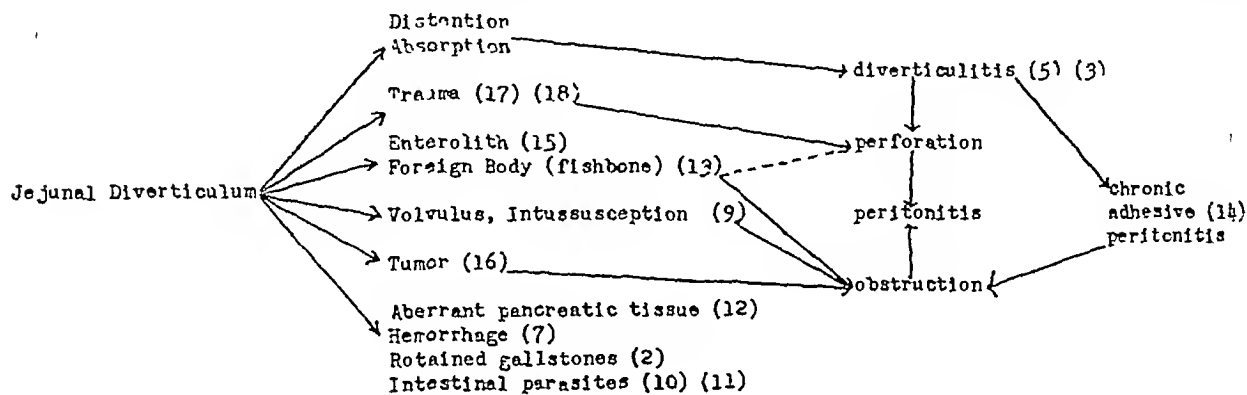
In those instances in which a jejunal diverticulum is discovered by X-ray localization of tenderness to the lesion by palpation under fluoroscopic control, observation of period of retention, and elimination of other explanations for the clinical symptomatology are necessary in the evaluation of the individual case. Observation, repeated examinations, and attempted control by diet and antispasmodics are in order before surgery is advised. The importance of distinguishing jejunal diverticula from duodenal diverticula in the course of the X-ray examination should also be empha-

sized. In those cases in which the diverticulum does not fill promptly when reached by the barium meal, this may at times be quite difficult and may depend chiefly on the greater mobility of the jejunum. In such cases the use of a Miller-Abbott tube in association with barium may prove helpful. The great technical difficulty of the surgical management of many duodenal diverticula with the resultant high mortality is usually sufficient to contraindicate such treatment except in the most urgent case. The surgical management of jejunal diverticula, because of the ease with which they may be mobilized, is a much simpler procedure and, in the absence of acute sepsis, the morbidity and mortality should approach that of interval appendicitis. There should therefore be no reasonable objection to the operative treatment of such cases in which the symptoms are sufficient to warrant a laparo-

and that a period of dietary restriction usually gave her relief.

Physical examination revealed a poorly nourished white female with slight generalized abdominal sensitiveness and an area of slightly greater tenderness immediately to the left of the navel.

Laboratory examination: R.B.C. 4,710,000, Hgb 90%, W.B.C. 9,450, Diff. neutrophils 72%, stabs 12%, segments 60%, eosinophils 2%, monocytes 8%, and lymphocytes 18%. The urinalysis was negative. The Kahn was negative. A gastric analysis revealed 36 degrees free acid and 20 degrees combined acid 45 minutes after an Ewald meal. A barium meal revealed a negative esophagus, stomach, and duodenum. Small intestinal films at one, two and three hours after the Ewald meal showed a pear shaped pocket of retained barium in the left abdomen at about the level of the navel. At four hours only a trace of barium persisted at this point. Re-examination indicated



tons, and in which the diverticulum is probably the etiological factor.

CASE REPORT

A 38 year-old white female was seen on 12-11-41 complaining of pain, cramping and drawing in character, located slightly to the left of the navel and coming at intervals, which began in May, 1941.

Her family history was negative for allergy, tuberculosis, diabetes, and epilepsy. Her mother was quite nervous, but the family was otherwise generally healthy. She had one child ten years of age.

She was said to have been well and healthy until fifteen years before the present illness when she was said to have had "flu passing into typhoid." She was treated for this with numerous purgatives and following this developed gaseous distension, constipation, and rather large amounts of mucous in the stools. Since that time she had continual abdominal discomfort and stated that she had not had a single bowel movement without medication or enemata. During this period she was treated at several Springs and Sanatoria with varying periods of relief.

In May, 1941, she gradually began to develop pain in the left abdomen which at first was drawing in character and gradually became cramplike, although, when severe, was persistent and unchanging in character. This pain came in paroxysms of varying degrees of severity which would last for hours or days, and which would come at intervals of weeks or months. Associated with the pain was moderate tenderness localized to the left of the navel. The patient ascribed this pain to her colon and felt that she obtained partial relief from metamucil and enemata

that it required from 45 minutes to an hour for the pocket to fill. The tenderness was localized to the pocket on fluoroscopic manipulation.

The patient was placed on a program of dietary control, sedatives, and antispasmodics. There was some improvement in her general condition. Her bowel function became reasonably adequate without laxatives or enemata. The spells of distress continued to recur, however, and she elected to have surgical intervention. This was done on 7-6-42 by one of us (G. W. W.). The sac was found about 8 inches distal to the ligament of Treitz and was embedded in the mesentery. It was about 3 cm in diameter. The sac was removed and the small stump inverted with a purse string suture. In the mesentery adjacent to the sac were two quite large firm lymph nodes. Others of this type were not seen elsewhere in the mesentery. Examination of the remainder of the abdomen was negative. Microscopic examination of the wall of the cyst revealed a marked eosinophilic and lymphocytic infiltration and the absence of a muscle layer.

The patient has apparently been relieved of her discomfort by this procedure. The presence of the enlarged lymph nodes and of the eosinophilic infiltration were taken as indicating a subacute diverticulitis which would tend to confirm the relationship between the diverticulum and the presenting complaints.

CONCLUSION

A case of jejunal diverticulitis is presented which was observed on X-ray examination and proven by surgical localization and removal. A brief discussion is made of the clinical significance of these lesions.

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Gastric Acidity in Pulmonary Tuberculosis*

By

ALFRED L KRUGER, M D

JFRSLA CITY NEW JFRSLA

IN the past three years, we have had occasion to study the gastric secretions in 325 patients with all forms of pulmonary tuberculosis. In addition, approximately 70 per cent of this group had gastro-intestinal X-ray studies to determine the presence or absence of pathology in order to note whether there was any correlation between the two findings.

It is not the purpose of this paper to enter into a discussion of the various test meals now in use. Suffice it to say that a test meal was desired for the fractional study of the gastric secretion which would be simple to use but yet offered effective stimulation. The reason for the necessity of a fractional study was twofold, its greater accuracy due to the individual variability of the acid secretion insofar as the time element is con-

those without any free acid in all specimens were classified as achlorhydria.

This series of cases has been subdivided into four groups, the classification conforming to the standards set by the National Tuberculosis Association: (1) minimal lesion—24 cases, (2) moderately advanced lesion—52 cases, (3) far advanced lesion—206 cases, (4) far advanced lesion complicated by amyloidosis—43 cases.

DEGREE OF ACIDITY

Minimal lesion. Of the 24 patients in this group, there were 11 males and 13 females. The ages varied between 16 and 36 years. There was found an incidence of 16 per cent achlorhydria, 8 per cent hypoa-

TABLE I
Incidence of degrees of acidity in pulmonary tuberculosis

	Total	Achlorhydria		Hypoa-		Normal		Hyper-	
		Male	Female	Male	Female	Male	Female	Male	Female
Minimal	24	1	3		2	6	6	4	2
Moderately advanced	52	1	2	4	5	10	14	7	9
Far advanced	206	18	33	17	31	34	29	30	14
Amyloidosis	43	5	10	2	4	9	9	4	25
Total	325	25	48	23	42	59	58	45	

cerned in reaching the peak of the acid curve, and because of the importance of determining whether or not patients with pulmonary tuberculosis have an increased latent period for the secretion of acid. Our test meal consisted of 100 cc of 7 per cent alcohol passed into the fasting stomach through an Ewald tube after a fasting specimen had been collected. Samples of the gastric juice were then taken every 15 minutes for 1½ hours. For convenience and ease of comparison with the reports of previous investigators, a set of similar standards was adopted, namely, normal free acid levels being between 20 and 40 degrees. Any case with acidity below this level was considered as hypochlorhydria, any above, as hyperchlorhydria and

acidity. Unfortunately, the group is much too small to take these results as evidence of the real values which might have been obtained if the number of cases had been larger.

Moderately advanced lesion. In this group of 52 patients, 22 were males and 30 were of the female sex. Here, the ages ranged between 15 and 45 years with the exception of one man who was 64 years old. There was an incidence of 6 per cent achlorhydria, 17 per cent hypoa-

Far advanced lesion. In this group of 206 cases, there were 99 males and 107 females. There was a fairly equal distribution of cases throughout all the age groups (the ages ranging between 10 and 70 years). Here, 24 per cent showed an achlorhydria, 23

*From the Hudson County Tuberculosis Hospital, Jersey City, N. J.
 B. S. Pollak, M.D., Medical Director, 100 Clifton Place.

per cent hypoacidity, 30 per cent normal acid and 21 per cent hyperacidity

Far advanced lesion complicated by amyloidosis In all of the 42 patients, the diagnosis of amyloidosis was confirmed by a 100 per cent congo red dye retention in the plasma in one hour and by the presence of an albuminuria. There were 20 male patients and 23 female patients with the ages ranging between 15 and 54 years. Thirty-five per cent of these cases showed an absence of free hydrochloric acid, 15 per cent showed hypoacid levels, 41 per cent a normal acidity and 9 per cent, a hyperacidity.

PEAK OF ACID CURVE

In the 20 minimal cases that showed free acid secretion, 19 reached the height of their acid curve within one hour. Of the 49 cases of moderately advanced tuberculosis, 35 reached their peak of acid se-

TABLE II

Incidence of degrees of acidity in cases with fever

	Total Cases	Achlor	Hypo	Normal	Hyper
Slight febrility	42	7	7	20	8
Moderate febrility	39	13	12	12	2
Marked febrility	4	2	1	1	

cretion within one hour. In the far advanced group of 159 patients and in the amyloid group of 28 patients, 117 and 21, respectively, showed their maximum acid secretion within the one hour period of observation.

FEVER

The temperature charts of all the cases were then analyzed with the viewpoint of determining what factor the temperature played in the degree of acid secretion. Any repeated rise in temperature for one month prior to the analysis was recorded as a case with fever, a fever under 100.5 was classified as slight, between 100.5 and 102 degrees as moderate and any rise above 102 degrees as marked. Of the entire group of 325 patients, 240 had a normal temperature. Forty-two fell within the slight fever class, 39 within the moderate fever group and 4 cases had a marked febrile course. The incidence of achlorhydria in the slight, moderate and markedly febrile groups (table II) was found to be 17 per cent, 33 per cent and 50 per cent, respectively.

ANEMIA

All of the patients had a red blood count and hemoglobin determination done about the time of the gastric analysis. A patient was classified as having a significant anemia if his red count was less than four million or his hemoglobin was found to be lower than 75 per cent (Sahli). Of the entire group, 60 cases fell within this classification. When subdivided according to the degree of their gastric acidity, it was found that 13 had an achlorhydria, 15 a hypochlorhydria, 21 had normal acid values and 11 had a hyperchlorhydria.

INTESTINAL TUBERCULOSIS

Of the entire group of 325 patients, 226 had a gastro-intestinal roentgen study. Of this number, 103 patients were found to have X-ray evidence of an

ileocecal spastic filling defect to suspect an intestinal complication. As can be seen from Table III, there was a marked similarity in the number of cases in all of the acid groups.

DISCUSSION

It has been the experience of practically every investigator working with the various test meals, that a certain percentage of the normal population will show an absence of free hydrochloric acid in their gastric secretion. Ruffin and Dick (1) in a study of 1917 controls and using an alcoholic meal with histamine stimulation found an incidence of 11 per cent achlorhydria in their series. Bennett and Ryle (2) studied the gastric secretions of 100 healthy medical students without symptoms and found 4 per cent achlorhydria. Sandroni and Sagal (3), using an Ewald meal with fractional specimens after 45 minutes, found an incidence of 7.5 per cent. Eggleston (4) noted an incidence of 10 per cent achlorhydria in a study of 2730 cases with gastric symptoms using a fractional meal.

Many of the earlier studies on gastric acidity in pulmonary tuberculosis were on too few cases to be of statistical importance (Brieger (5), Munson (6)). In more recent investigations, Cohen (7), in a study of 300 patients with tuberculosis, using an Ewald meal, found an incidence of 7 per cent achlorhydria in minimal lesions, 6 per cent in moderately advanced lesions and 8 per cent in far advanced cases. In other words, his results are approximately that which one would find in normal, healthy controls. Gray and Melnick (8) in a study of 50 cases with advanced tuberculosis found that 24 per cent of their cases had an achlorhydria. Perla (9) in a review of 198 patients found an incidence of 10 per cent achlorhydria.

Our results are at some variance with the above findings. Unfortunately, the number of minimal cases is much too small to draw conclusions from but 16 per cent showed an absence of free hydrochloric acid. In the moderately advanced group there was found an incidence of 6 per cent achlorhydria. In the far advanced group without and with amyloidosis, there was found a decided increase in the number of patients showing an absence of free hydrochloric acid, 24 per cent of the former and 35 per cent of the latter pre-

TABLE III

Incidence of degrees of acidity in patients with and without intestinal tuberculosis

G. I. X ray	Total	Achlor	Hypo	Normal	Hyper
Positive	103	22	18	39	24
Negative	123	27	20	41	26

sents this finding. So, we note that as the disease becomes more progressive and the duration of illness increases, the percentage of patients with achlorhydria rises from a normal level in moderately advanced cases to an incidence of 35 per cent in patients with far advanced disease complicated by amyloidosis. This finding is in accord with the conclusions of Robin and DuPasquier (10) but in disagreement with the findings of Perla (9).

Townsend (11) in a study of 61 normal healthy students using alcohol as a test meal found that the

greater proportion of the cases reached their acid peak at 60 minutes. In the subjects studied, 75 per cent showed a lower figure for free hydrochloric acid after the 60 minute specimen. In 32 of the cases that had a free acid of 50 degrees or more, 30 of them reached their peak within one hour. In a study of 85 non-tuberculous male individuals who complained of vague gastro-intestinal symptoms with no evidence of gastric or duodenal ulceration on roentgen examination but who showed free acid in their secretions, 72 per cent reached the peak of their acid curve within the 60 minute specimen. Approximately 95 per cent of the minimal, 71 per cent of the moderately advanced, 73 per cent of the far advanced and 75 per cent of the amyloid patients in this series of cases reached their acid peak within one hour. As these results are similar to those found in normal individuals, it is not felt that there is an increased latent period in the secretion of acid in patients with tuberculosis.

Munson and Perla found that the presence of fever had no relation to the secretion of acid by the stomach in their studies on tuberculous patients. Cohen on the other hand found that the percentage of achlorhydria among patients with fever is about $3\frac{1}{2}$ times as high as among those without fever and therefore concluded that fever, per se, causes a diminution of gastric acidity. In reviewing our cases who showed a normal temperature (240 patients), it was found that 21 per cent showed an achlorhydria and 19 per cent a hypochlorhydria. On the other hand, in an analysis of the remaining 85 cases who showed some degree of fever, there was found an incidence of 25 per cent achlorhydria and 23 per cent hypochlorhydria. In comparing the two results, we find no significant degree of difference. However, when a closer analysis is made of the degree of fever present (Table II), it is found that as the temperature approached higher levels, the greater was the incidence of anacidity.

The factor of anemia and gastric acidity has been the subject of much controversy. The consensus of opinion has been that the absence of free hydrochloric acid causes an impaired intestinal iron absorption with resultant hypochromic anemia (12, 13, 14). In the group of 72 patients with achlorhydria, 13 or 18 per cent showed a significant anemia. This figure coincides very closely with the number of patients in the entire group of 325 cases that showed an anemia, namely, 60 cases or 18 per cent. Therefore, we could not find here that achlorhydria, per se, played a significant part in the development of anemia. In an analysis of the cases without anemia, it was found that 23 per cent showed an absence of free acid. This was similar to the group of 60 cases with anemia who showed an incidence of 22 per cent achlorhydria. Hence, in this series of patients, we were unable to find any justification to assume that anemia, per se, had any influence on the degree of acidity.

Straus and Wurtz (15) found that the tubercle bacillus will not lose its virulence after six hours ex-

posure to the gastric juice. Inkster and Glovne (16) later demonstrated that gastric secretion will not destroy tubercle bacilli in the sputum after ninety minutes exposure. Gray and Melnick in a study of 42 patients, found tubercle bacilli in the gastric contents more frequently in the anacid and hypacid groups but admitted that this was not due to the bactericidal powers of the gastric juice. A gastro-intestinal roentgen study was done on 226 of our patients. Of the 103 cases that showed roentgen evidence of intestinal tuberculosis, 21 per cent were found to have an achlorhydria, whereas, of the 123 normal cases, 22 per cent were noted to lack free acid. This result is in complete accord with the observations that the presence or absence of free hydrochloric acid in the stomach is of no significance as to the finding of tubercle bacilli in the gastric secretions or in the development of intestinal tuberculosis.

Although the purpose of this report was to investigate the gastric response in terms of free acid, titrations were also made for total acidity. In all of the cases, the figure for the total acidity was from 3 to 25 degrees higher than that for free acid. This is in close agreement with the observations on normal subjects by Townsend who found a difference of 4 to 18 degrees. We agree with her and others that when free acid is present, the estimation of the total acidity is of no practical importance.

We are cognizant of the fact, as emphasized by Sagal, Marks and Kantor (17) that there is a definite tendency in older individuals to show a diminution or loss of free acid. This factor, however, played a minor role in this series of patients as 279 of them were under the age of 50 years. Of the 46 cases above the age of 50, only 11 showed an achlorhydria and 9 of these were in the far advanced stage of the disease.

As will be seen from Table I, the incidence of achlorhydria was twice as great among female patients as it was among the male cases. Sagal, Marks and Kantor as well as Ruffin and Dick found that gastric acidity in females is definitely lower, the difference in the former group of cases being almost 10 degrees in both the free and total ranges.

CONCLUSIONS

1 The gastric acidity of 325 patients in various stages of pulmonary tuberculosis was studied and it was found that as the degree of the disease progressed, the incidence of gastric anacidity increased.

2 Significant fever caused an increase in incidence of achlorhydria.

3 Anemia, per se, did not affect the degree of acidity.

4 There is no increased latent period in the secretion of acid, the gastric response following a normal pattern.

5 The presence or absence of free acid played no role in the development of intestinal tuberculosis.

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Notes On Nutrition

1943 brings new knowledge of marginal dietary deficiencies as well as a better understanding of the human requirement of amino acids, better knowledge of the food requirements of mothers and infants, new techniques for the nutritional teaching of lay and special groups. The nations of the world who now are suffering food shortages will benefit by our newer knowledge of nutritional science.

There is some experimental foundation for the theory that vitamin lack favors susceptibility to infections and recently it was found that animals fed high protein diets withstood infection better than those on low protein diets (*J. Pediatrics* 20 475 1942). On the other hand it was found that Vitamins A and C had no influence on the immunological factors in influenzal and pneumococcus infections (*J. Clin. Invest.*, 21 121, 1942). There is no reason to overdose people with vitamins in the effort to prevent infections, and yet probably the nutritional status as a whole is important in resistance to infection.

From dog feeding experiments it was inferred that the minimum nicotinic acid requirements of a 70 kilo man should be about 10 mg per day. Also it was confirmed that sulfapyridine inhibits the curative action of nicotinic acid and that fresh liver counteracts this inhibition (*J. Biol. Chem.*, 144 679, 1942).

Effects of Blanching on Vegetable Nutrients It was found that blanching—in boiling water for one, two or three minutes, tenderizes the vegetables and reduces their volume, thus making canning more efficient. In small units of large surface area about 20 per cent of sugars, minerals, protein and Vitamin C are lost while in larger roots, while the loss in Vitamin C is about the same, the sugars, proteins and minerals average only 10 to 15 per cent loss (*J. Soc. Chem. Ind.*, 61 96, 1942).

Industrial Nutrition and the War Dr. Borsook is correct in emphasizing the need for better food for war workers but it is questionable if the method of administering artificial vitamins is as good as improving the foodstuffs eaten. It is pointed out that, even after all the publicity given to the needs for greater milk drinking during the past 20 years, there has been only a per capita increase of about 5 to 7 per cent (*Am. J. Pub. Health*, 32 523, 1942).

Reconstituted Milk today is merely dehydrated whole milk in powder form shaken up with the proper quantity of water. It should be sold in areas where natural milk of proper hygienic standard is not easily obtainable, but should be labelled to distinguish it from other milks. The skim milk used in reconstituted milk ought to be dehydrated at a temperature of 150 degrees F or less (*Bulletin, N. Y. Acad. Med.*, 18 488, 1942).

Thiamine in Stone Milled Flour By using an old American flour mill bread was made from wheat and the bread assayed for thiamine, and about 5.2 micro-

grams per g was found present. The high thiamine content was attributed to the presence of a significant proportion of the aleurone layer of the wheat berry (*Cereal Chem.*, 19 529, 1942).

The Evaluation of Nutrition Surveys Dietary studies can furnish no more than presumptive evidence on the prevalence of malnutrition. The word "malnutrition" should be used only where body abnormalities arising from nutritional causes exist. There is not as yet any standard conception of exactly what an adequate diet is, and the food composition tables are not standardized either. The earliest symptoms of malnutrition are often vague and most certainly are not diagnostic of any particular deficiency disease or of malnutrition itself (*Am. J. Pub. Health*, 32 406, 1942). However, dietary studies furnish the best means now available to uncover likely areas of malnutrition before severe degrees of deficiency have developed.

Dehydrated Meat A drying unit can produce about 1000 lbs of dehydrated beef in one hour, but only about 600 lbs of dehydrated pork in one hour owing to the higher fat content of pork. Dehydrated beef contains 55 per cent protein, 30 per cent fat and 10 per cent moisture. Dehydrated pork contains 50 per cent protein, 40 per cent fat and 10 per cent moisture. The pork product is less stable than the beef product. Very little is known about the nutritive changes which dehydration may produce in meat but this subject is under study now (*Food Industries*, 14 47, 1942).

The Incidence of Dental Caries Out of 2 million men examined for selective service 1 million were rejected for general military service. Of these about 450,000 were qualified for limited military service. Dental deficiencies accounted for 20.9 per cent of the 900,000 who were rejected for general service. No other single condition approaches this figure. A high incidence of dental caries in children in the Canal Zone has been found and is thought to be due to the composition of the drinking water in large part. The subject of dental caries presents a challenge to nutritional investigators.

Vitamin A and Liver Diseases The liver being the principal storehouse for Vitamin A abnormalities of the metabolism of Vitamin A occur when the liver is damaged. Often, in such cases, the blood carotene is not as low as the plasma Vitamin A, due, possibly, to the fact that, in cirrhosis for example, there is an impairment of the conversion of carotene to Vitamin A (*J. Clin. Invest.*, 21 309, 1942). Vitamin A is taken up faster and released more slowly by damaged liver cells than by normal liver cells (*Proc. Soc. Exp. Biol.*, 50 266, 1942). Hence in giving Vitamin A to persons with damaged livers the dose should be large so that the healthy cells will receive some of it. In cancer of

the GI tract with impaired liver function it is almost impossible to raise the plasma level of Vitamin A even by the parenteral injection of from 50,000 to 150,000 USP units daily (Ann Int Med, 16 221, 1942)

Oxidative Destruction of Vitamin D In the case of live stock feeds, added Vitamin D, in whatever form used, or no matter how it is premixed, undergoes serious oxidation of such a degree that in one to three months no potency is left (J Ind Eng Chem, 34 979, 1942)

Nutrition in Pregnancy The People's League of Health in Great Britain make a report on some interesting clinical experiments with the feeding of pregnant women, followed by comparison of the course of pregnancy in cases where special food supplements were added and in cases where no food supplements were added to the diets of mothers. The added food supplements consisted of iron, calcium, minute amounts of iodine manganese and copper, Vitamin B complex, Vitamin C and halibut liver oil. Of 1530 primiparas receiving the supplements, 54 per cent showed toxemia, as shown by albuminuria. Of 1512 primiparas who received no supplement, 74 per cent showed the toxemias (Lancet, II 10, 1942)

Riboflavin in Cereal Grains and Bread Riboflavin losses during the baking of bread are relatively insignificant. There are greater varietal than environmental differences in the amounts of riboflavin in wheats. Yellow corns were found to have the same amounts of riboflavin as white corn. Marquis wheat was high with 132 micrograms per gram while rival wheat was low with 106 micrograms per gram (Cereal Chem, 19 55, 1942)

Thiamine and White Blood Cells There is typically a greater concentration of ascorbic acid, thiamine, niacin and riboflavin in the leucocytes and platelets of the blood than in the erythrocytes and plasma. Thiamine is higher in leucemic than in normal leucocytes and is abnormally metabolized by leucemic cells. This applies to the three types of leukemia—myeloid, lymphatic and monocytic (J Clin Invest, 21 161, 1942), (Ibid, 21 177, 1942)

Anemia in British Women and Children on Wartime Diets A broad survey of the hemoglobin readings of 1074 persons of all ages in England indicated an increased incidence of anemia as a result of wartime diets. In children—between 6 and 12 months of age the reading averaged 75.4 per cent, from 1 to 2 years of age, 72.8 per cent, and between 4 and 5 years of age 81.4 per cent. The Haldane scale was used, in which 100 per cent is equal to 13.8 g of pigment for each 100 ml of blood, which is a lower standard than used in the U. S. A. All these values were regarded as pathological because they can be increased by iron administration. It was suggested that the decrease in hemoglobin of women and children should be combatted by educational means and by the provision of iron supplements, particularly for babies and children (Lancet, II 32, 1942)

Intestinal Microorganisms Destroy Ascorbic Acid The effect of aerobic and anaerobic cultures of various intestinal bacteria upon ascorbic acid, indicated that *E. Coli* and *A. aerogenes* decomposed ascorbic acid, whereas *Proteus* and *Alcaligenes*, growing in pure culture failed to destroy ascorbic acid, and even protected it from oxidation by air. The presence of glucose or lactose in the media exerted a sparing action on ascorbic acid. In cases of severe colitis or

diarrhea, it is best to administer ascorbic acid parenterally (J Bact, 44 75, 1942)

Stability of Vitamin B₁ During Baking The loss in thiamine, regardless of its source is proportional to the time required in the baking. All sources of thiamine, during a normal bake showed a loss of about 20 per cent. The highest loss is in the crust. Toasting of bread leads to a further loss of thiamine ranging from 11 to 25 per cent. Toast as usually prepared contains about 15 per cent less thiamine than the original bread (Cereal Chem, 19 532, 1942), (Ind Eng Chem (Anal Ed) 14 35, 1942)

Cirrhosis of the Liver and Nutrition Portal cirrhosis is probably not caused by the direct effects of alcohol, but by dietary deficiencies associated with chronic alcoholism, because cirrhosis can be produced in animals by deficient diets and because in cirrhosis of the liver, the administration of high protein diets, Vitamin B complex and choline favorably affect the course of the disease (J Clin Invest, 20 481, 1942). The use of high protein diet supplemented by Vitamins A and D and a daily dose of 1 gm of choline chloride caused very marked improvement in many cases of portal cirrhosis in man, often causing a cessation of the abdominal ascites, a return to a more nearly normal albumin-globulin ratio of blood plasma proteins and increased hemoglobin readings (J A M A, 118 1403, 1942). In cases of cirrhosis where hepatic damage is not too far advanced, the use of a high protein, high carbohydrate, low fat diet, with abundance of Vitamins A and D, and frequent injections of liver extract produces very marked improvement and even clinical recovery (Am J Dig Dis, 9 115, 1942). The intravenous injection of a 15 per cent amino acid solution daily for 4 weeks, along with a low fat diet and comparatively high protein and high carbohydrate diet caused very marked subjective and objective improvement in a small group of cases (J Lab Clin Med, 27 1400, 1942). At the present time, although neither the animal nor the clinical experiments give us reason to formulate any definite theory as to the cause of cirrhosis, they do offer a working method which, even empirically holds out much more hope than ever before of being able to help the patients.

Vitamin C and the War The injection of ascorbic acid in a concentration of 100 mg per kg of body weight, immediately following trauma which would otherwise prove fatal, will save life (Nature, 149 637, 1942). British scientists are studying the loss of ascorbic acid in preparations of citrus foods for table use because of the scarcity of these sources of ascorbic acid in wartime. Some authors see no need to use more than basal requirements of ascorbic acid (Biochem J 35 1240, 1941). Possibly ascorbic acid when given at once in large amounts in conditions of shock has a pharmacological action rather than a nutritional one. Ascorbic acid has been variously recommended for hay fever, heat prostration, lead poisoning, Heineken reactions, and even insomnia. These and many other instances in which ascorbic acid administration has been recommended are perhaps not properly supported by objective data and are decidedly confusing, even though some of the work has a large suggestive value.

British Food Production The Ministries of Food and Agriculture in England set out to make every acre produce 5 per cent more food than formerly in order to save 1,000,000 tons of shipping, and this has actu-

ally been accomplished by, (a) plowing up grasslands, (b) adjusting livestock breeding and feeding programs, (c) improving farm management and (d) applying scientific methods generally. Soil analyses, and the establishment of 13 advisory centers with the agricultural staff in each county, has resulted in the reclamation of thousands of acres of unproductive soil (Science, 96 360, 1942)

Saccharin The perennial question as to whether or not the daily use of saccharin can cause any trouble seems to be answerable in the negative, inasmuch as it is excreted unchanged and has no food value, and

does not cause indigestion unless taken in inordinate amounts (J A M A., 119 344, 1942)

Post-war Europe which will be in a very bad state from the standpoint of food deficiencies will need particularly two foodstuffs which will go a long way toward meeting the situation—wheat and dried milk, or dried skim milk and dehydrated butter (Nature, 149 182, 1942)

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Editorials

ALCOHOL AND PUBLIC OPINION

DWIGHT ANDERSON, LL B Director of Public Relations of the Medical Society of the State of New York, in a recent article* notices an alleged public apathy toward scientific information on alcoholism. He feels that if the public are to be stimulated into social action on behalf of the problem drinker they must be emotionally indoctrinated with the idea that the drunkard is a sick man who can be helped, and who is worth helping. The public indoctrination must begin with the medical profession and the health authorities as well as the public. He rightly believes that the medical profession are pessimistic and indifferent toward the problem drinker and he gives evidence to prove that the patient's propensities, arising from the depths of consciousness, show that he belongs to the psychiatrist and to the properly specialized hospital. A more hopeful attitude on the part of the profession generally might bring about an increased percentage of cures, and serve the purpose of public indoctrination with the concept of illness. Dr Anderson thinks that a sympathetic identification on the part of the doctor is the first essential in this program.

No doubt Dr Anderson is right, even though he admits that he is dealing with a problem filled with almost unique difficulties. He realistically knows that prohibition of the sale and manufacture of alcohol for beverage purposes will never work. The public are really not indifferent to the findings of science in most subjects, but in the matter of alcoholism, the public is prejudiced and fears that a motive of moral uplift is behind the publication of the discoveries of science. This is because they regard the drunkard as an immoral man and not as a sick man. They feel that family tragedies caused by alcoholism in one of the family betrays a man who is so selfish that he neglects his family for the sake of his own addiction. Therefore any attempt to whip up public interest in the problem of alcoholism falls flat. Unfortunately, drunkenness contains for the public an unavoidable element of the comic, especially where incoordination is present. Normal drinkers are prejudiced in favor of the custom of drinking and gain some personal sense of superiority from the spectacle of a drunkard.

The general practitioner has very little success in attempting the cure of addictions, and until the curri-

cula of the medical schools contain basic training in psychiatry, and until the doctor can get a fee proportional to the time consumed in psychological study of a patient, he can do little more than refer the case to a psychiatrist. Since few drunkards are wealthy, and since few localities possess a psychiatrist, the need of public institutions for the problem drinker is obvious.

No doubt many physicians do regard the drunkard sympathetically even though the families of the drunkard usually do not. To them he is primarily a selfish person who deserves little sympathy. If there were more cases of alcoholism than there are, and if each case provoked more widespread social havoc than it does, the public could more readily be aroused to a partial solution of this disease.

The public may be influenced by the adoption of the correct attitude toward the drunkard by the physician, and come to believe, as all doctors now believe, that alcoholic addiction depends upon a deep psychological maladjustment of the individual to the demands of society. However, this is a long, drawn-out method, which by itself might never effectively enlist public sympathy or interest. There is a specific relationship between the kind of distortion of consciousness which alcohol produces and the psychic needs of the problem drinker. This is proved by cures in which the patients do not adopt other addictions of a different type. It follows that the fewer persons who drink alcohol at all, the fewer addictions will result. Such a change in the ecological field is admittedly impossible through banning alcohol for beverage purposes. However, there is an evolutionary tendency toward teetotalism in communities in which there never has been any attempt to restrict drinking. In 1818 a certain town of one thousand population had 20 saloons, but by 1918, although the population had grown to ten thousand, there was only one saloon. Yet there had never been any legal restriction or moral persuasion beyond the Women's Christian Temperance Union and the efforts of a few churches. In 1918 neither young men nor women were much interested in drinking, partly because the one remaining saloon had an unsavory atmosphere, and because their attention was not directed to the subject of alcohol. We may hope for great improvement in alcoholism from this very evolution of taste, but in a period of history where the social unit is under unprecedented economic, political and moral tension, we fear that alcohol will find in-

*Alcohol and Public Opinion, quarterly Journal of Studies on Alcohol, Vol. III No. 3 December 1942.

creasing use. For that reason, any method would be welcomed which could move the public to action on behalf of the drunkard. Possibly the greatest help may come from the very source of which Dr. Anderson appears dubious—the publication of scientific discoveries. If the results of psychoanalysis of the problem drinker could be popularized without factual distortion in magazines of large circulation, and with sufficient frequency, the public would eventually understand the particular helplessness of the men who find spurious mental salvation in alcohol.

THE URINARY EXCRETION OF NICOTINE BY SMOKERS

NOW that Peail has shown that between the years of 30 and 50 one out of five heavy smokers dies before his time many men are wondering how they can still enjoy their cigarettes and not lose their lives.

One way perhaps is not to inhale the smoke. H. B. Hoag and P. S. Larson of the Medical College of Virginia showed last year that a non-inhaling smoker excreted in his urine only one-tenth as much nicotine as was excreted by an inhaler smoking the same number of cigarettes. This agrees with the observation that a non-inhaler retains only one-tenth as much nicotine as is retained by an inhaler.

The impression gained from the studies made by Doctors Hoag and Larson was that only from 2 to 8 per cent of the nicotine retained in the body after smoking 40 cigarettes a day is excreted in the urine. The rest must be destroyed in the body.

A POSSIBLE TREATMENT FOR ASCARIS WORMS

JULIUS BERGER and C. F. Asenjo reported in Science for April 19, 1940, that bromelain obtained from fresh pineapple juice will digest Ascaris worms in vitro. A similar effect was obtained years ago with strong commercial preparations of papain (Meich),

from derived from figs, and also a preparation made from Papaya juice.

The question is if a sufficient concentration of these substances can be maintained for long enough in the bowel, and if so, whether they would have advantages over the anthelmintics now available.

DO ATHLETES DIE YOUNG?

ONE often hears that athletes injure their heart and hence tend to die before their time, but able heart consultants have doubted if this is true.

In 1941, the Metropolitan Life Insurance Company made some studies which showed that college athletes have a life expectancy near that of their classmates in general, and better than that of men accepted for Standard insurance. Curiously, the men who played baseball had the highest mortality—7 per cent higher than the average of all college athletes. The crew men came next with a mortality 3 per cent over average, which one might have expected because rowing is one of the most exhausting of all exercises. Track athletes and football men had an average mortality. Interestingly, the lowest mortality was found among men who had their letter in more than one sport.

A POSSIBLE TREATMENT OF DIARRHEA

IN the April 19, 1940 number of Science, McCay and Smith of Cornell University, Ithaca, New York, reported that tomato pomace, or the dried residue left after the making of commercial tomato juice, when fed to dogs with diarrhea promptly caused a drying of the feces. The amount of pomace fed amounted to 5 per cent of the wet ration of the animals.

This effect may be something like that produced by feeding scraped apple or Karaya gum. At any rate, it ought to be investigated further because gastro-enterologists could well use more drugs that would help patients with unexplained types of diarrhea. Medicine is woefully weak in this field.

Abstracts of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

JEGNIERS, H. *Medical Progress Nutrition. The Appearance of the Tongue as an Index of Nutritional Deficiency.* New Eng. J. Med., 227, 221, Aug., 1942.

An excellent review of different forms of glossitis with vivid descriptions of the pictures seen and a comprehensive account of their anatomy. The appearance of the tongue in pellagra, in riboflavin-deficiency, in

pernicious anemia, in Vitamin A, and other deficiencies is described. The symptoms caused by these forms of inflammation of the tongue are discussed. Other forms of glossitis, especially atrophic gastritis, are mentioned and their etiology and treatment are discussed. At the end the author gives a systematic survey of the diagnoses the practitioner should make after the inspection of the tongue.—Rudolf Schindler

BOWEL

BURTON, C. C. AND BLOTNER, C. *Sliding and Other Large Bowel Hernia.* Ann. Surg., 116, 394, Sept., 1942.

Sliding hernias of the large bowel are the most serious, the rarest and the most difficult to repair. Walton defines a sliding hernia "as one in which some portion of the wall is formed by a viscus which in its normal position is only in part covered by peritoneum." Two dangers

in the repair of such large bowel hernias which the authors emphasize throughout the article are cutting into the bowel unwittingly thinking it is the hernial sac and compromising the circulation to the bowel by dividing the vascular or medial leaflet of the mesentery. In a consecutive series of 2614 repaired inguinal hernias, 68 or 2% were of the large bowel and 54 of the latter were of the sliding variety. The pathogenesis of the various types of such sliding hernias are then taken up in detail and the surgical procedures for their repair elaborated upon. Hernioplastomy is discussed although the authors do not advocate use of this procedure. Forty-three primary sliding hernias of the large bowel, followed post-operatively for a period of 34 months showed a recurrence rate of 6.9%—Frank Neuvelt

SLATTERY L R AND HINTON, J W *Mortality Rate from Acute Appendicitis in a Municipal Hospital Am J Surg 56 294, Aug, 1942*

Because the morbidity and mortality factors in acute appendicitis and its complications are of great concern, the authors investigated the case records of 677 patients operated upon at Bellevue Hospital between 1928 and 1939. Their mortality rate of 5.1 per cent compares favorably with other hospital reports and strikingly the rate dropped in the second period to nearly half of that in the earlier period. The greatest rate of decrease was in the acute cases and in those with general peritonitis. The experience of the operators did not beneficially influence the mortality rate because the majority of cases were operated upon by the house staff. There were twice as many men as women patients and about 25 per cent had had previous attacks of this disease. Abscesses operated upon within the first 5 to 6 days have a higher death rate than those with an average of 10 days duration. No definite conclusions could be drawn as to the role of cathartics in deaths from appendicitis. The McBurney incision offers a more favorable response and it appears that somewhat better results were obtained when removal rather than drainage alone was undertaken in appendiceal abscess. The principal cause of death was peritonitis which accounted for 27 of the 35 fatalities.

The diagnosis of appendicitis is not without difficulties. Nausea and vomiting are more important symptoms than pain in causing the patient to seek medical aid. Tenderness and rigidity was present in only 30.1 per cent of the 677 cases and rectal tenderness in 47.5 per cent. The leucocyte count is of limited diagnostic value and the temperature may be misleading. It is erroneous to assume that the lowered mortality of neutro-

appendicitis in any institution in recent years is due to any one factor—Michael W Shulkin

BRAITHWAITE, L R *The Ileogastric Syndrome Brit J Surg, 30 15, July 1942*

According to Braithwaite, the events which concern the ileogastric syndrome have to be divided in two parts. (1) Those arising in the gastric area, producing phenomena in the ileo-cecal region i.e. the "gastric-ileal" reflex. This is a true nerve reflex, a normal sequence. When food enters the stomach, the contents of the lower ileum is poured into the cecum.

(2) Those events arising in the ileocecal region giving rise to symptoms in the "gastric" area, and probably of pathological origin, the "ileogastric syndrome" proper.

Three conditions can cause this syndrome, but it might be that other pathological conditions in the same region might be recognized in later times. Braithwaite mentions the three following causes and their roentgenological differential diagnosis. (1) Chronic appendicitis or appendix dyspepsia. There is definite localized roentgenological evidence of pathology in the appendix and spasm of the ileocecal valve. (2) Single chronic ileocecal adenitis. Spasm of the lower ileum and of the ileocecal valve. (3) Chronic tuberculous adenitis. Roentgenological evidence of glands, spasm of the lower ileum and of the ileocecal valve. In all three conditions the epigastric signs of pyloric spasm with hypersecretion, hyperacidity and delayed or non-appearance of bile in the stomach may be the same—Franz J Lust.

FLYNN J M *Adenocarcinoma of the Ileum Am J Roent Rad Therapy, 48 168, Aug, 1942*

Flynn reports a case of adenocarcinoma of the ileum causing intestinal obstruction. In his case there was a partial obstruction yielding roentgen evidence of the condition. The author reviews some of the literature and discusses the diagnosis of the condition—Maurice Feldman

GARDNER C E, JR. AND SAPP, C J *Atypical Features in the Manifestations of the Acutely Inflamed, Nonruptured Appendix Am J Surg, 57 477 Sept 1942*

In this critical analysis of 500 cases of acute unruptured appendicitis the authors reveal the frequency of atypical manifestations. The age incidence in the series reveals that one patient in fifteen is under 10 and over 50 years of age. The onset may begin concurrently with or during the course of acute infections and degenerative diseases. 4 cases occurred

In patients hospitalized for other conditions. Pain was not the first symptom in 1 out of every 12 cases, instead first symptoms include nausea, anorexia, burning sensations, general malaise, diarrhea, vomiting, headache, backache and abdominal distension. In 10 per cent of the cases the pain remained generalized. One in every 6 complained of neither nausea nor vomiting. Constipation was present in 34 and diarrhea in 16 of the 500 cases. Fever, though a common symptom, was absent in 22 per cent, but in 24 patients rectal temperatures of 102.2 degrees F or higher were present. The urine revealed red blood cells in one out of every 17 patients. Abdominal tenderness was elicited in all, and where rectal examination was done tenderness was present in 85 per cent. An increase of muscle tone of any degree was absent in 33.4 per cent of the cases. Atypical features of appendicitis occur often and these must be recognized if the mortality is to be lowered—Michael W Shulkin

VOLDENG, K E *Locating Acute Appendicitis Prior to Surgery Am J Surg, 57 519, Sept, 1942*

The following plan is presented as a means of executing a more direct approach to the inflamed appendix and thus avoiding unnecessary exploration and subsequent complications. Following the diagnosis of appendicitis the patient is prepared for surgery with the pre-operative medication of morphine, atropine and a barbiturate. The action of these drugs is evident in the operating room prior to making the incision because of the absence of rigidity and secondary tenderness and a mentally relaxed patient. At this time discrete tenderness is usually found directly over the appendix and occasionally an indurated structure can be palpated through a thin abdominal wall. The surgeon can apply the proper type of incision to the overlying point on the abdomen and facilitate removal, drainage if necessary and in general simplify the appendectomy. A full and accurate clinical history will further assist in this procedure—Michael W Shulkin

LEIGH O C, JR. *Ileus Associated with Edema of the Bowel S G O, 75 279, Sept 1942*

Leigh points out that true inhibition of the motor activity of the bowel is present in only 2 types of cases—those associated with lesions of the spinal cord or retroperitoneal space, and those accompanied by edema of the bowel. In the latter cases, rapid deflation can best be accomplished by riding the bowel of edema and restoring small intestinal activity. In ileus small bowel motility

has been found to be depressed as a result of edema of the bowel. In most cases, this edema appeared to aggravate existing partial mechanical obstructions. Therapy directed toward raising the plasma protein concentration will restore small bowel activity and aid in the deflation of the patient. —Robert Tuell

IMPINK, R R AND CLAMMER, G R *Atresia of the Duodenum Ann Surg, 116 334, Sept, 1942*

The number of reported cases of duodenal atresia is small. "This is a report of a case of congenital atresia of the duodenum in an infant 30 hours old. Roentgenologic examination proved the atresia to be complete. A duodenojejunostomy was performed 50 hours after birth. The child had attacks of respiratory difficulty which recurred with increasing frequency after the second post-operative day. On the fourth day post-operatively the wound was found disrupted. Liquids taken by mouth were retained in one-half to one-third the ingested amounts, and there was evidence that the anastomosis functioned. The wound of the abdominal wall was re-sutured on the sixth day following the first operation. Three hours later the infant died. Autopsy showed the anastomosis to be intact. Bilateral pneumonia was the cause of death." —Frank Neuvelt

LIVER AND GALL BLADDER

CARRYER, H M AND SWANSON, V F *Evaluation of Acetylation of Sulfanilamide as a Test of Liver Function, Proc Soc Exp Biol Med, 50 339, June, 1942*

It is a known fact that in man, the body detoxicates aromatic amines by means of acetylation. As sulfanilamide in the urine is excreted in a state of only partial acetylation it was thought that varying percentages in the amount of the acetylated drug might reflect the state of liver function. Small amounts of sulfanilamide were given to normal subjects and to subjects known by accepted tests of liver function, peritoneoscopy, surgical exploration and, in some cases, necropsy, to have hepatic disease. Urine was collected for 24 hours following the administration of the drug. It was evident that the proposed test did not have any definitely apparent value in the determination of liver function or in the detection of hepatic disease. —H Necheles

O'SHEA, M C *Stones in the Ductus Choledochus An Analysis of 2,602 Cases of Biliary Tract Disease at St Vincent's and Harlem Hospitals in Their Last 250,065 Hospital Admissions Am J Surg, 56 279, Aug, 1942*

There is a recognized high percentage of stones in the common duct

though this varies greatly and in proportion to the number of common ducts that are explored and drained routinely. His analysis of incidence is drawn from the combined admissions of two hospitals for ten years which total 250,065 patients. Of these 2,548 had cholecystitis with 1,204 revealing biliary calculi. One hundred and one or 4 per cent had stones in the common and hepatic ducts. Operation upon 1,855 cases of cholecystitis disclosed common duct stones in 62 per cent while the ducts were drained in 77 per cent of this series.

The indications for exploration and drainage of the common duct in cholecystitis and cholelithiasis are the presence of cholangitis, palpable stone in the duct, jaundice, murky bile on aspiration and dilatation of the common duct. Surgery in these cases should not be hasty nor delayed, but rather attempted when the patients' biochemical and fluid balance have been re-established. The complications which occurred in this series include hepatitis, cholangitis, jaundice, cirrhosis, pancreatitis, external and internal biliary fistulae, strictures, perforations and intestinal obstruction by impaction of the ileum with a gall stone. The author records a case history with the last mentioned complication and another record of a patient spontaneously passing a retained common duct stone with nitrites, atropine, fatty meal and bile salts. —Michael W Shutkin

SURGERY

BARRY, H C *Fibrous Stricture of the Small Intestine Following Strangulated Hernia Brit J Surg, 30 64, July 1942*

The author reports three cases of late intestinal stenosis following a strangulated hernia. Occasionally, although a strangulated loop of intestine is viable, as shown by the return of its colour, pulsation in its blood vessels and peristaltic waves there is such an extensive damage to the inner layers that complete resolution cannot take place. Fibrosis occurs either at the site of the constriction or throughout the length of the strangulated intestine, and leads to the formation of an annular and tubular stricture. This is especially likely to occur when there has been an extensive haemorrhagic infiltration of the strangulated intestine and its mesentery. Clinically a few days after operation, diarrhea with blood in the stools is sometimes noticed. Weeks, months, or even years later the signs of a slowly progressive small intestinal obstruction develop and at laparotomy a fibrous stenosis at the site of the old strangulated loop is found. —Franz J Lust

MAYO, C W AND SCHLICKE, C P *Anuria After Operations on the Colon*

and Rectum J Urol, 48 207, Aug, 1942

Urologic complications following operation on the colon and rectum occur frequently. Many of the patients have uroinfections prior to operation. Operative manipulation, such as mobilization of the right colon may compromise the right ureter and a similar operative procedure on the opposite side may expose the left ureter. In dissection of the rectum and rectosigmoid, direct injury to the bladder or urethra may occur and at times may produce a fistula. Trauma to the prostate gland and seminal vesicles may cause post-operative epididymitis. The ureters may be accidentally cut, crushed or ligated. Considerable of the posterior support of the urinary bladder is removed and its nerve supply is injured making evacuation of the bladder very difficult. These factors interfere with the free drainage of urine and invite infection.

The authors reported 5 cases of anuria which occurred at variable times after radical operation for carcinoma of the colon or rectum. In 2 cases anuria was apparently due to post-traumatic edema and crystalluria as well as to an inadequate intake of fluids. The patients recovered promptly after ureteral catheterization. In the third patient anuria was due to sulfonamide chemotherapy. The fourth patient developed anuria as a result of dehydration. The fifth case represented an example of intrarenal anuria and ended fatally. —Robert Tuell

PATHOLOGY

POPPER, H STEIGMANN, F AND DYNIEWICZ, H A *Distribution of Vitamin A in Experimental Liver Damage Proc Soc Exp Biol Med, 50 266, June, 1942*

The Vitamin A content of cirrhotic livers is low but in acute human and experimental hepatitis normal amounts are found. The blood Vitamin A level in acute hepatitis, however, is low and hemeralopia appears. Histologically in human cirrhosis and hepatitis the Vitamin A distribution is markedly altered, the total amount is often reduced. To explain these alterations the histologic Vitamin A distribution in experimental liver damage was studied. Rats were intoxicated with various doses of carbon tetrachloride. The organs were examined for Vitamin A by fluorescence microscopy. Some livers were also chemically examined for Vitamin A. Vitamin A was found in damaged but not in uninvolved liver areas. The pathologic areas take it up faster and release it slower than normal ones. High Vitamin A therapy replenished the uninvolved areas. —H Necheles

GREENSTEIN, J P AND ANDERVONT, H B *The Liver Catalase Activity of Tumor-Bearing Mice and the Effect of Spontaneous Regression and the Removal of Certain Tumors* *J Nat Cancer Inst*, 2 345, Feb., 1942

The liver catalase activity of mice bearing various tumors was determined and found to be much lower than normal. The slow growing tumors did not show this effect until late in their development. The effect of the tumors on decreasing the liver catalase was found to be progressive with the growth of the tumors. Mice after regression of a tumor were resistant to a growth of a second inoculum of the same tumor—and, subsequent to the second inoculation, the liver catalase of these mice remained at the normal level. Mice were inoculated in the tail with sarcoma. The tumors grew more slowly than in the skin and the decrease in the liver catalase activity at corresponding times was less in the caudally inoculated than in the cutaneously inoculated mice. At 16 days after implantation the tails were amputated. The liver catalase activity decreased still further following this operation but by the second day was nearly normal, and by the third day and subsequently thereafter was not a completely normal level. The return of the liver catalase value to the normal level following removal of the tumor is similar to the results obtained previously using rats bearing subcutaneously implanted hepatic tumor.

The results presented in this and earlier papers indicate that the liver catalase system of rats and of mice, with few exceptions, is depressed by the presence of a tumor in these animals. That this effect is readily reversible is attested by the fact that removal of the tumor or a regression of the tumor is followed in a comparatively short time by a restoration of the liver catalase value to the normal level. Reduction of enzymatic activity from one-tenth to one-twentieth of its normal value indicates that a rather profound effect has occurred and suggests that some toxic material given off during growth of the tumor travels to the liver and affects the catalase system with the results shown. The well-known cachexia of cancer must have some biochemical basis and it may be that this phenomenon constitutes a contributing factor. It must be emphasized, however, that not all the liver enzyme systems of tumor bearing animals are affected in this way. It would appear so far that the effect of a tumor in an animal is most marked on the liver catalase.—H Necheles

GREENSTEIN, J P JENNETTE, W V AND WHITE, J *The Liver Catalase Activity of Tumor-Bearing Rats and the Effect of Extirpation of the*

Tumors *J Nat Cancer Inst* 2 288, Dec., 1941

The liver catalase activity of rats carrying the Jensen sarcoma at 3 weeks and of rats carrying the transplanted hepatic tumor No 31 at 4 weeks, is about one-tenth that of normal rat liver. Extirpation of the hepatic tumor caused a rapid restoration of the liver catalase activity which reached the normal level between 24 and 48 hours. Inoculation of a second tumor in animals from which the first tumor had been removed caused again a drop in liver catalase activity to the level produced by the presence of the first tumor at an equal stage of growth. Removal of the second tumor produced the same rate of restoration of the normal level of liver catalase activity as did removal of the first tumor. The catalase activity of the first and of the second tumor was the same. Starvation from 1 to 3 days produced no appreciable effect on the liver catalase activity of either normal or of tumor-bearing rats. Rat livers regenerating in animals bearing the transplanted hepatic tumor had a liver catalase activity of the same order as non-regenerating livers in animals bearing this tumor. Removal of the tumor caused a rapid restoration of the liver catalase activity to the normal level.

The effect produced by the presence of the transplanted tumor has been tentatively interpreted as being due to the elaboration by the tumor of a toxic material which travels by way of the circulatory system to the liver and there causes directly or indirectly a lowering of the catalase activity. The thymonucleopolymerase activity of the spleens of rats bearing the transplanted hepatic tumor was compared with that of the spleens of normal animals. Despite the fact that the spleens of the former are about double in size and in weight those of the latter, the activity of this enzyme in both was practically identical.—N Necheles

MAVER, M E, MIDER, G B, JOHNSON, J M AND THOMPSON, J W *The Comparative Proteinase and Peptidase Activities of Rat Hepatoma and Normal and Regenerating Rat Liver* *J Nat Cancer Inst*, 2 277 Dec., 1941

A comparative study was made of the proteinase and peptidase activities of two tissues, hepatoma and regenerating liver, which were derived from hepatic cells. The proteinase activity of rat hepatoma extracts, using hemoglobin as substrate, was greater than that of normal or of regenerating rat-liver extracts. Also di-leucylglycine was hydrolyzed much more rapidly and extensively by the peptidase preparations from hepatoma tissue than by the peptidase preparations from the normal or regener-

ating hepatic tissues. This definite acceleration in both the proteinase and the leucylpeptidase activity suggests that the nitrogen metabolism of the hepatic tissue was altered when it became neoplastic, and this change in the nitrogen metabolism favored a more rapid growth rate in the tumor.

During the first 3 days after partial hepatectomy, which included the period of most rapid proliferation, the average proteinase activities of the regenerating livers appeared to be slightly less than those of the normal liver extracts. On the fourth and seventh day after the operation the average proteinase activities were slightly above those of normal hepatic tissue.—H Necheles

EDWARDS, J E AND DALTON, A J *Induction of Cirrhosis of the Liver and of Hepatomas in Mice with Carbon Tetrachloride* *J Nat Cancer Inst*, 3 19, Aug., 1942

A report on the induction of hepatomas in mice by repeated oral administration of carbon tetrachloride, appeared in an earlier paper. Repeated oral administration of carbon tetrachloride in olive oil to mice which were autopsied when they were 1 year of age or less, resulted in a hepatoma incidence of 88.2 per cent. This is distinctly above the incidence of spontaneous hepatomas in these strains. The tumors were well-differentiated hepatomas and resembled the spontaneous and o-aminazo-toluene-induced tumors of the mouse. One tumor of eight, in which transplantation was attempted, is transplantable. The benignancy or malignancy of the hepatoma has not as yet been established. Single or limited doses of carbon tetrachloride in concentrations sufficient to cause hepatic necrosis failed to induce tumors. However, if the same total amount of carbon tetrachloride was given in divided doses over a period of 2 months, hepatomas developed in 71 per cent of the mice. In the livers of carbon tetrachloride-treated mice there is an abundance of a canary-yellow pigment which is, perhaps, a conjugated lipid.—H Necheles

PHYSIOLOGY SECRETION

CODF, C F AND VARCO, R L *Prolonged Action of Histamine* *Am. J Physiol.* 137 225, Aug., 1942

In response to 15 to 60 mgm doses of histamine in beeswax mixture, the gastric pouches of dogs secreted gastric juice for twenty four or more hours. The juice secreted during this time varied between 683 and 1,570 cc and its hydrochloric acid concentration ranged from 0.49 to 0.54 per cent (134 to 149 degrees free hydrochloric acid in the customary clinical units).

Gastric Acidity, Nutritional Hydration and Appetite^{*}

By

FREDERICK HOELZEL
CHICAGO, ILLINOIS

In a study made upon myself, primarily to determine whether a relation exists between the desire to eat and the acidity of the contents of the fasting stomach, it was found that a restriction in the protein intake increased the acidity and protein re-alimentation or a high protein intake reduced it (1). It was also found that 1 or 2 days of fasting in 1925 increased the gastric acidity as did periods of protein restriction but, in two fasts of 33 and 41 days, the gastric acidity decreased again after the first few days. The decrease in acidity after an initial increase in prolonged fasting was the opposite of what was expected on the basis of the effect of simple protein starvation but, as the gastric acidity after the prolonged fasts rose above the peak which appeared during the first few days of these fasts, this was heretofore regarded as evidence that the net effect of prolonged fasts was to increase the gastric acidity, like short fasts and simple protein restriction (1).

In contrast to the findings in fasting 1 or 2 days in 1925, data secured recently (1942) showed that the acidity of the contents of my fasting stomach was decreased by single-day fasts. In the recent study, one determination of the fasting gastric acidity was made every morning. Before 30 single-day fasts (and with only one day of fasting per week to assure complete recovery between fasts), an average of 0.090% free HCl was found, after the fasts, an average of 0.052% HCl was found. The difference between the effects of short fasts in 1925 and 1942 did not appear to be due to mere differences in the prefasting protein intakes and/or prefasting levels of gastric acidity. It seemed more likely that a change in the general nutritional condition, as a result of aging and/or other factors, accounted for the decrease in acidity produced by the recent fasts. In short, the recent prefasting nutritional state appeared to be in some respects similar to the condition after the first few days of fasting in the prolonged fasts of 1925. The gastric acidity then also decreased with further fasting but it still remained to find an explanation of that decrease.

A study of heretofore largely neglected data, which were obtained in 1928 and involved a period of undernutrition (without fasting) and also of subsequent re-alimentation, suggested a simple explanation of all of the observed effects of fasting as well as of variations in the food intake on gastric acidity. A state of undernutrition was produced in 1928 by moderately restricting the total caloric intake to get rid of a small deposit of fat. Earlier attempts to get rid of fat by restricting the food intake or by fasting generally became complicated by the development of nutritional or post-fasting edema and the edema, in turn, seemed to become a factor in the subsequent restoration of the fat deposit. In 1928, a carbohydrate restricted diet, relatively high in fat as well as in protein, was re-

garded as of special value in controlling nutritional hydration (2). With about 2500 calories daily of this diet, body-weight, gastric acidity and the general state of hydration were maintained at relatively low but fairly constant levels. With a reduction of the food intake, first to about 2200 calories and later to about 1800 calories daily, weight declined gradually, as indicated in Fig. 1. The gastric acidity did not decrease much at first but, after about 3.5 kg. in body-weight were lost, free acid practically disappeared from the fasting gastric contents. Then, during a period of 20 days (in July—Fig. 1), no free acid was found on 15 days and only traces on the other 5 days. With the onset of this period of gastric hypoacidity, the carbohydrate restricted diet also no longer appealed to the appetite. An attempt was made to increase at least the tolerance for protein by adding HCl to the meat which was included in the diet (ground meat which was soaked in 0.5% HCl was swallowed without being chewed) but the acidified meat proved to be irritating to the digestive tract and the added HCl did not restore free acid to the fasting gastric contents. As the tolerance for fat as well as for protein had reached its limits and extreme fatigability suggested the need of a larger amount of carbohydrate in the diet, the total caloric intake was increased mainly by increasing the carbohydrate intake. As a result, nutritional hydration with some degree of grossly evident edema developed but free acid reappeared and increased in the fasting gastric contents and the appreciation of protein and fat was correspondingly increased. The abrupt and periodic variations in the food intake, which are indicated in Fig. 1 (mainly during August), were made in alternate attempts to reduce or limit the extent of the edema and improve the general nutritional condition.

In any case, the results indicated that the fasting or basal gastric acidity varied more or less directly with the degree of hydration of the organism. This also suggested that the decrease in gastric acidity which occurred after the first few days of the prolonged fasts was due to the dehydrating effect of starvation and that the increase in acidity after the prolonged fasts was related to the post-fasting hydration or edema. Moreover, the effects of variations in the protein intake on gastric acidity could be similarly explained. The role of protein in regulating the degree of hydration of the organism has become clear from studies on nutritional edema. Protein deficiency promotes hydration and was found, in my study, to increase gastric acidity while protein re-alimentation or high protein intakes reduce hydration and gastric acidity. The hypoacidity produced by the period of undernutrition in 1928 (Fig. 1) was apparently due to the combined dehydrating effects of semi-starvation, a relatively high protein intake and carbohydrate restriction. One or two days of fasting in 1925 undoubtedly served

^{*}From the Department of Physiology, University of Chicago.

mainly as periods of protein restriction in increasing the gastric acidity, as the fasting then always followed periods involving high protein intakes. The average recent prefasting weight (57.5 kg) was similar to the weight after 13 days of fasting during the 41-day fast in 1925 (3) and the recent prefasting protein intakes were also lower than in 1925. It is therefore not surprising that the gastric acidity recently decreased with only one day of fasting as it did in 1925 after a few days of fasting. Incidentally, it might be mentioned that, with re-alimentation and re-hydration or the development of slight transient edema after the recent single-day fasts, the gastric acidity rose again above the prefasting levels.

A relation between the secretion of acid gastric juice and the degree of hydration or the water and salt balances might perhaps also have been inferred from

gastric acidity. Besides this, the sugar content of edema fluid (5) and the effects of high carbohydrate intakes (2, 6), particularly after fasting or after periods of undernutrition, indicate that carbohydrates can, to some extent, serve like NaCl and/or other salts in determining the general degree of hydration and gastric acidity.

In 1925, the desire to eat, as well as the gastric acidity, increased with 1 or 2 days of fasting. Recently, however, I was generally less inclined to eat after one day of fasting than before fasting and the decrease in gastric acidity helped to explain this. In other words, the recent observations confirmed the earlier finding of a relation between gastric acidity and the desire to eat, more specifically, between gastric acidity and protein-hunger (7, 8, 9). Moreover, the finding of a relation between gastric acidity and the degree of

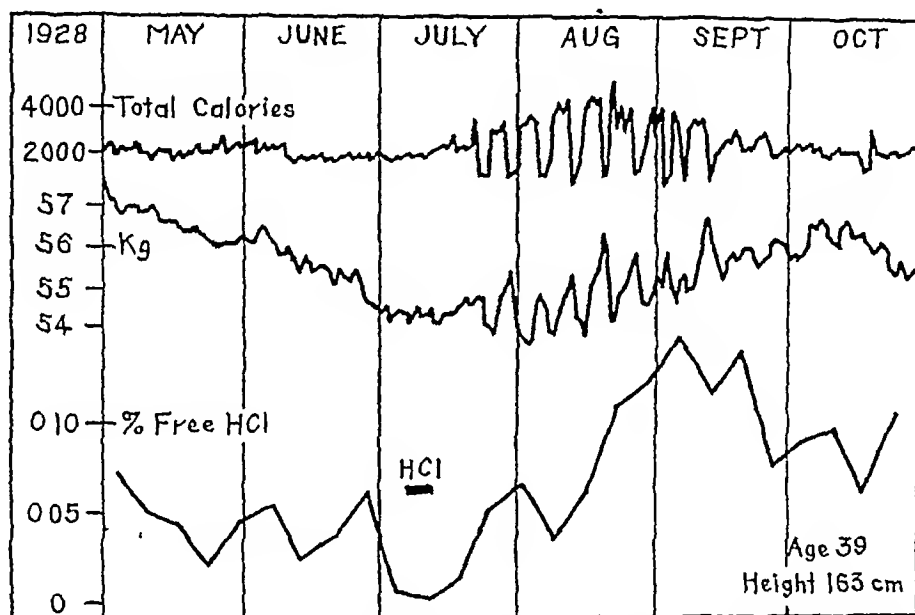


Fig 1 Showing the effect of undernutrition with a diet relatively high in protein and fat and of re-alimentation with a higher carbohydrate intake on gastric acidity. Top curve = total calorie intake, middle curve = body-weight and bottom curve = weekly average free HCl of fasting gastric contents (one determination daily). Period of use of acidified (HCl) meat during July indicated by "HCl" bar (0.10% HCl = 27.4 clinical units).

the consideration that the acid gastric juice is mainly water with 0.5% or less of HCl and that the HCl is evidently derived from the organism's main chloride, NaCl. Ivy found that water drinking increased the gastric acidity (4). This was confirmed by my observation that the gastric acidity was increased as a result of drinking 500 cc of water on the 20th and 35th days of my 41-day fast in 1925. As the desire to eat increased when the gastric acidity increased, it became my policy to avoid drinking more water while fasting than what was demanded by thirst. After my 41-day fast, it was found that a high salt intake (20 gm NaCl on each of 2 days), following a period of salt restriction, sharply increased the gastric acidity (1). Data concerning body-weight (3) indicated that the salt increased the gastric acidity without having increased general hydration (Table I). The water balance and the salt balance can therefore function more or less as independent variables in influencing

hydration also seems to explain why appetite often decreases as a result of undernutrition or fasting, when the actual need for food is increased. This otherwise puzzling consequence of food restriction was clearly noted when I fasted every other day about 2 months in 1919, over 3 months in 1923 and 5 months in 1927. A condition similar to chronic undernutrition was produced in each instance and the desire to eat decreased enough within the first few weeks to cease to be a problem after that. There was no evidence that a decrease in the periodic hunger contractions accounted for the decrease in the desire to eat but, in 1927, daily determinations of the gastric acidity were made and showed that the acidity decreased. However, the extent of the decrease depended also on the type of diet that was used on the days of eating between the days of fasting. In 1927, vegetarian, carnivorous and mixed diets were tried during separate periods in the 5 months of fasting every other day and the main

findings were that diets which prevented the development of edema or helped to reduce hydration produced gastric hypoacidity and gastrogenic (or proteinogenic) diarrhea while diets which failed to prevent the development of some degree of edema left the gastric acidity somewhat higher and prevented diarrhea. Similarly, when fasting every other day in 1919 the diet was relatively high in protein and prevented edema but severe diarrhea developed while in 1923, more carbohydrate was used and edema became a complication but diarrhea did not develop. This indicates that, as a result of the dehydration and decrease in gastric acidity incident to severe undernutrition (or ieng), the ability to utilize food as well as the appe-

also involved in determining the intake of other nutritional essentials

SUMMARY

Data secured during a period of undernutrition and of re-alimentation revealed a relation between the fasting gastric acidity and the degree of general hydration. Such a relation also explains changes in gastric acidity which were found to occur in connection with short fasts, prolonged fasts and variations in the protein intake. A relation between gastric acidity and hydration likewise explains decreases in appetite and in food tolerance which were found to be produced by restricting the food intake too much or by too frequent fasting.

TABLE I

Showing effect of NaCl intake on body-weight and on the acidity of the fasting gastric contents

Date	Weight kg	Number of Half Hourly Gastric Aspirations	Per Cent Free HCl			Remarks
			Lowest	Highest	Average	
1923 Sept						
20	52.7	1	0.07	0.16	0.107	After one week of NaCl and protein restriction following 41-day fast
21	53.9	0				NaCl and protein restriction continued
22	53.9	5	0.09	0.25	0.160	NaCl and protein restriction continued
23	54.6	7	0.07	0.22	0.129	NaCl and protein restriction continued
24	55.7	0				NaCl and protein restriction continued
25	55.2	5	0.14	0.21	0.160	NaCl and protein restriction continued
26	56.1	2	0.17	0.19	0.180	NaCl and protein restriction continued
27	56.6	6	0.04	0.18	0.123	After two weeks of NaCl and protein restriction
28	58.0	6	0.14	0.26	0.235	After 20 gm NaCl taken on previous day but with continued protein restriction
29	58.4	-	0.14	0.36	0.256	After another 20 gm NaCl taken on previous day but with continued protein restriction

tite may become impaired. In this connection, it should, of course be borne in mind that the pH and volume of the gastric, pancreatic and other digestive secretions are likely to be modified by dehydration like the fasting gastric acidity.

Finally, it should be understood that the decreases in the desire to eat and the other complications which arose in my experiences were mainly consequences of deliberate restrictions of the food intake. After the periods of deliberate food restriction, the unrestrained appetite generally led to food intakes which overcompensated for previous losses. My observations support the findings of Richter and of Young (10) that appetite tends to indicate basic and specific needs, especially after fasting. It could hardly be otherwise if physico-chemical mechanisms such as appear to be involved in the regulation of the protein intake are

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Observations on Starvation Diets and Hunger Ketosis*

By

GEORGE F. DICK, M.D., MARTIN G. GOLDNER, M.D.

and

THOMAS P. SINGER, S.M.

CHICAGO, ILLINOIS

DIABETIC ketosis and ketosis in hunger and starvation have the same cause (1). Need for carbohydrates, either because not enough is available (hunger) or because the power for its utilization is impaired (diabetes) compel the organism to draw most of its energy from protein and fat. But while the ketosis in diabetes tends to be severe, progressive and leads to acidosis and coma, it is mild, stationary and self-limiting in hunger or starvation. Is this a quantitative difference only, so that ketosis in hunger would be the first and mild degree of a process which in its further development causes the severe syndrome in diabetes, or is the different course of their ketoses due to metabolic differences between the starving and the diabetic organism?

The concepts of fat metabolism and the mechanism of ketosis have changed considerably during recent years (2, 3). The old theories that fat and carbohydrate oxidation are linked together, that "fat burns in the fire of carbohydrates," that ketosis occurs when a certain relationship between ketogens and anti-ketogens is surpassed, and that ketobodies are toxic products of an abnormal metabolism have been abandoned or challenged. It has been seen that ketobodies are produced by the liver and utilized by the peripheral tissues; fat oxidation has been found not to be dependent directly from carbohydrate oxidation and limited only by the body's limited ability to burn ketones, the theory of multiple alternate oxidation (Hurtley) and the "beta-oxidation condensation hypothesis" (McKay) (3) have replaced Knoop's successive beta oxidation and Stadie's (4) aketonuric utilization limit for fat has been proclaimed as the limiting factor of ketosis instead of the F.A.G. (fatty acid: glucose) ratio of Woodjatt (5) and the K.A. (ketogenic: anti-ketogenic) ratio of Shaffer (6).

The following study is a clinical contribution to the problem of the mechanism of hunger ketosis. Findings on three patients who were kept on subcaloric diets for prolonged periods of time will be presented and a few of the older hunger experiments from the literature will be reviewed in an attempt to correlate clinical observations with the modern concept of fat oxidation.

Experimental procedure
Three obese non-diabetic patients who were willing to cooperate were placed on subcaloric diets for periods of 133, 25, and 32 days. They were confined to the metabolism ward of Billings Hospital but were permitted moderate hospital activity. Every day their body weight was noted and a qualitative urinalysis for ketobodies was done. The basal metabolism (BMR) and respiratory quotient (RQ) were determined twice weekly. Quantitative determinations of the acetone

bodies in blood and urine, estimations of CO₂ and pH in the serum, and of the blood proteins were done at various intervals. Van Slyke's method for the determination of the ketobodies was used. The results are expressed in mg acetone. For a period of time the nitrogen balance was determined in each patient, for this purpose five-day collections of urine and feces and of aliquot parts of the constant diet were analyzed. Glucose tolerance tests were performed in all three patients at the beginning and in two patients at the end of the observation period. In one patient the effect of insulin on the hunger ketosis was studied. The caloric deficit and the way in which this deficit was covered in each instance was calculated.

Results

Patient 1 (Mrs. S. L., No. 200423) was a 56 year-old housewife, who weighed 117.4 kg. She had an arterial hypertension of 192/120 but was not in circulatory failure and there was no evidence of kidney damage. She was under observation for 133 days, for the main period of 72 days her diet consisted of C 31 P 42 F 15—427 calories. This diet was preceded for one week by a diet of 600 calories and was followed for the remainder of the observation period by a diet consisting of C 22 P 54 F 27—547 calories. The nitrogen balance was studied for 92 days. The patient felt very well throughout the whole period, enjoyed her progress and complained about occasional headaches only. Her course is represented in Fig. 1, a summary of the more significant laboratory data is given in Table IA. The weight was reduced to 87.3 kg, which amounts to a loss of 31.1 kg or of 25.6% of the initial weight. Her blood pressure was lowered to 140/88. The basal caloric requirement dropped from 2100 to 1450 calories, a total decrease of 650 calories or 30.9 per cent. The patient was in nitrogen deficit, which, however, decreased with continuation of the diet. It reached its peak during the fourth week with 2.01 gm N per day. The blood proteins were always within normal limits. A mild ketosis developed slowly and showed a tendency to decrease during the second half of the observation period. The highest values were 25 mg per cent acetone-bodies in the serum and 1600 mg acetone-body excretion within 24 hours. The CO₂ and pH in the serum remained always within the normal range. The RQ varied between 0.72 and 0.67. The glucose tolerance tests before and after the observation period gave the following results:

	FBS	1/2	1	2	3 Hrs
Before	85	161	211	127	77
After	83	135	165	158	78

Patient 2 (H. S., No. 283912) (Fig. 2, Table IB), was a 58 year-old housewife who complained of backache and tiredness. She had a hypertension which with weight reduction fell from 168/104 to 132/74. She was

*From the Department of Medicine and the Chemical Division of the Department of Medicine, University of Chicago.
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TABLE I

	Patient and Diet	Days on Diet	Weight kg	BMR Cal	R Q	N Deficit	Blood Acetone mg %	Urinary Acetone mg	CO ₂ in Serum	pH
A	L 427 Cal	3	115.5	2100	—	—	—	—	—	—
		20	108.7	1070	0.69	1.60	10.03	—	27.1	7.40
		33	107.3	1850	0.70	2.01	—	—	26.8	7.51
		40	105.4	1760	0.68	1.71	16.4	1070	26.9	7.50
		49	103.4	1630	0.70	1.12	24.5	620	27.2	7.48
		58	101.1	1530	0.68	1.08	16.35	1580	24.6	7.50
		70	96.3	1500	0.70	1.21	16.2	1090	27.6	7.47
		101	90.6	1510	0.66	0.69	12.8	1154	27.0	7.48
B	Sp 508 Cal	2	130	1800	0.84	—	—	—	—	—
		15	123.5	1460	0.69	1.80	11.7	352	26.2	—
		21	122.2	1400	0.70	1.06	—	—	—	—
C	Ch 405 Cal	2	163.2	2380	—	—	—	—	24.6	7.35
		9	158	2370	0.71	2.63	11.8	1105	26.0	7.47
		16	154	2150	0.72	2.05	6.82	379	—	—
		23	152.4	2050	0.73	0.30	0.23	615	27.3	7.43

placed on a diet of 508 calories consisting of C 18 P 55 F 24 and reduced within 24 days from 131.2 kg to 121.8 kg, an actual loss of 9.4 kg or 7.2 per cent. The basal caloric requirement decreased from 1800 to 1390 calories, a loss of 23 per cent. The nitrogen deficit was less than 2 gm daily, and the RQ varied between 0.84 and 0.69. The blood proteins remained normal. The urine showed qualitative acetone tests on two days only, the amounts of ketobodies excreted and accumulated in the blood during this period were moderately higher than the normal values. The CO₂ in the serum was within the normal range. A glucose tolerance test in this patient was done only at the beginning of the observation period. The blood sugar was 84 mg per cent at fasting, reached 158 mg per cent one-half hour after the glucose meal, and fell to 86 and 73 two and three hours later.

Patient 3 (J Ch, No 200734) Fig 3, Table IC, was a 20 year-old female with the excessive weight of 163.2 kg. She had been obese all her life, but did not present any evidence of endocrine disturbances. After a first week on a 700 calories diet she was placed on 405 calories (C 24 P 48 F 13). During the 32 days of observation her weight was reduced to 148.8 kg, a total loss of 14.4 kg or 8.8 per cent. The basal caloric

requirement decreased from 2380 to 2050 calories, a loss of 13.8 per cent. The N deficit was determined from the eighth until the 24th day, it reached its highest value, 2.95 gm per day, in the second week, but decreased later to 0.3 gm per day on the same diet. The RQ varied between 0.74 and 0.71. Blood proteins and serum pH and CO₂ remained within the normal range. The blood ketobodies and the acetone-body excretion were somewhat increased but showed a tendency to level off towards the end of the period. The oral glucose tolerance tests at the beginning and after treatment showed the following insignificant changes of a slightly decreased tolerance:

	FBS	½	1	2	3 Hrs
Before	96	174	156	117	66
After	85	152	146	123	81

On two occasions 10 units of protamine zinc insulin were given and the 24-hour ketobody excretion as well as the fasting blood level of acetone bodies were determined on this and the preceding day. The results of both experiments were similar, though the changes were more pronounced in Experiment 2, the values of which are given here. 10 units of protamine zinc insulin lowered the post-absorptive blood acetone level from 9.23 mg per cent to 3.98 mg per cent and the

TABLE II

The caloric deficit, FA/G ratio and Stadie's aketonuric maximal utilization limit for fat (U_0) for the three patients

1	2	3			4	5	6		7	8	9			
Patient	Weight kg.	Diet			Basal Caloric Requirement Plus 20%	N Deficit gm	Caloric Deficit		FA/G Ratio	Body Fat Utilized gm	U gm for			
		P	gm C	F			Cal	Total			Covered by P F	Ideal Weight	Actual Weight	
L	107.6	42	80	13	405	2124	1.69	1710	40	1679	2.45	187	160	256
S	123	55	18	24	508	1740	1.89	1232	48	1184	2.24	131	160	300
Ch	166	48	24	18	405	2700	2.63	2295	60	2235	2.95	248	148	300

24-hour acetone body excretion from 615 mg to 257 mg. The fasting blood sugars were on the same level and the patient did not have symptoms of hypoglycemia at any time. This result demonstrates that insulin affects the ketobody metabolism in a non-diabetic organism as well as in the diabetic organism.

COMMENT

Most of our observations are confirmations of known facts and do not require extensive discussion.

1 *Weight* The weight loss in all three patients was very satisfactory, though all had claimed that reducing diets with and without thyroid medication had been unsuccessful in the past. This demonstrates simply that the failure to lose weight on subcaloric diets is not due to the diet itself but to lack of co-operation or supervision. Whatever the cause of obesity may be, there is no one who could not reduce on a reduction diet! The weight loss, however, was not a steady one. Though the weight curves as a whole showed a clear downward direction, the weights fluctu-

muscular exercise after a fast of 24 hours. The most significant values were found in the afternoon determinations. We determined the RQ in the afternoon six hours after the very small lunch which our patients were permitted to take. The values were somewhat lower than the morning values but still far above 0.65 and therefore insignificant. Neither could confirmation of Alberts and Dietrich's finding be found in Benedict's (11) famous protocols on a prolonged fast. The test person L fasted for 31 days and had daily exercises. But his RQ, though occasionally somewhat lower in the afternoon than in the morning, never fell below the range for fat oxidation.

4 *N deficit* It has been found in many hunger and starvation experiments that the nitrogen excretion is relatively high at the beginning and decreases markedly for a certain period with continuation of the protein fast (11). Our observations confirm this finding. The N deficit was not large in the beginning but decreased later, the blood proteins remained within normal limits. The organism apparently tries to main-

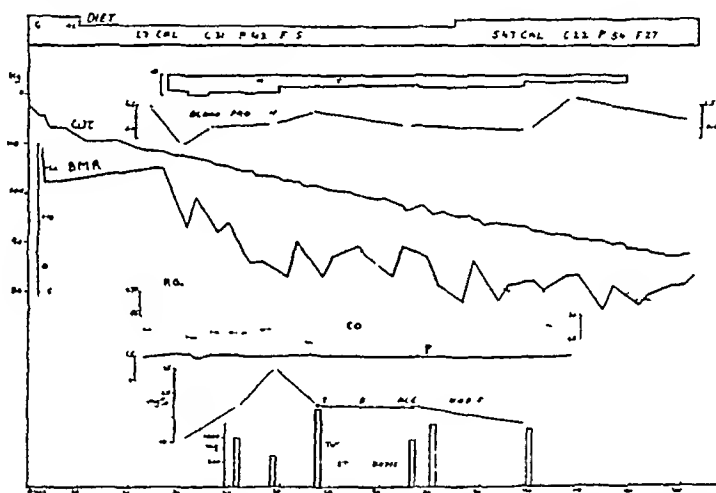


Fig 1 Patient S. L., course of body weight (Wt), basal metabolic rate (BMR), respiratory quotient (RQ), CO, and pH in serum, blood proteins, blood acetone bodies and acetone-body excretion during 133 days on subcaloric diet

ated around this general line and remained occasionally at exactly the same level for several days in spite of the constant diet. This phenomenon has been discussed very thoroughly by Newburgh (7).

2 *Basal Calories (BMR)* The fact that the basal caloric requirement decreased more rapidly and in a greater degree than the weight is another significant finding (8, 9). The relationship between the percentages of loss of body weight and of basal caloric requirement of our patients was the following:

Patient 1 25.5/30.9 Patient 2 7.2/23 and Patient 3 8.8/13.8

3 *The Respiratory Quotient* The RQ was low in all our departments and varied between 0.73 and 0.68. This proves again that the metabolic mixture consisted mainly of fat. However, no values were obtained which were so low as to indicate carbohydrate formation from fat. This is in agreement with most investigators. Recently, however, Alberts and Dietrich (10) have reported experiments in which they obtained values of 0.60 and 0.58 in persons who had done

tain or approach a normal N balance for as long as possible (12). If no protein is offered, it spares its own protein until—in the final stage of starvation—no other substance but protein is available for heat production and then a complete breakdown of the body metabolism occurs (13).

5 *Acid/base Balance* The CO₂ and pH in the serum was normal throughout all three observation periods. Even in complete starvation no change in the pH value of the blood was observed. Benedict (11) found the same values for CO₂ at the middle and at the end of the 31 days' fast in his subject L.

6 *The Ketobodies* The ketobody excretion and the blood level of ketobodies have been studied since Zuntz's (14) and Biugsch's (15) hunger observations. Ever since, it has been found that only a mild ketosis occurs in starvation, and that, instead of increasing this ketosis will level off or even decrease. Whereas our three obese patients showed a mild degree of ketonemia and ketonuria, occasionally no ketosis at all has been observed in obese patients on similar subcaloric

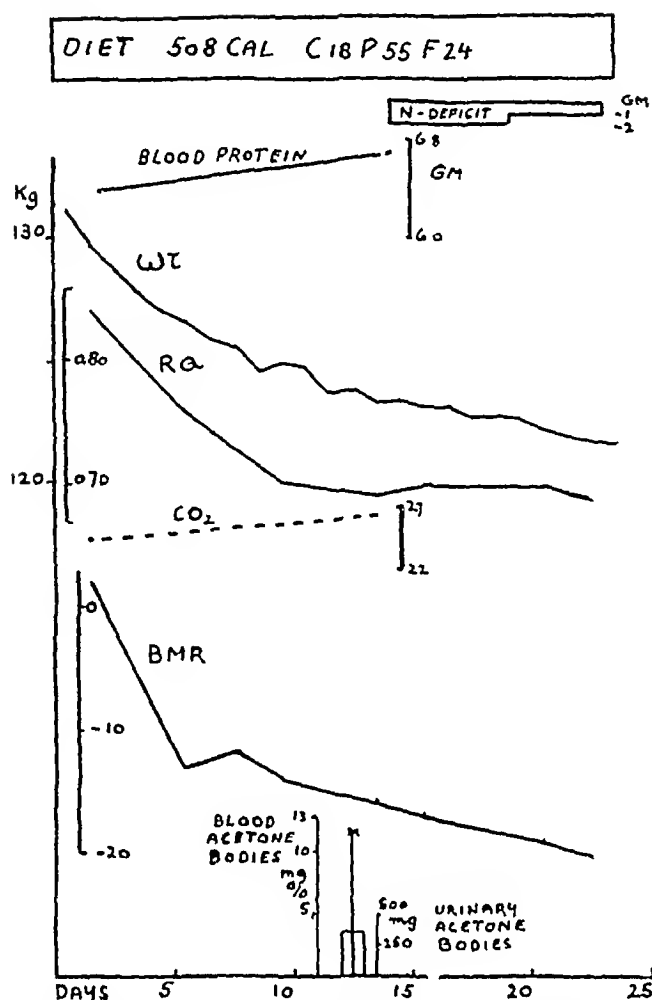


Fig 2 Patient H S, course of body weight (Wt), basal metabolic rate (BMR), respiratory quotient (RQ), CO_2 and pH in serum, blood proteins, blood acetone bodies, and acetone-body excretion during 24 days on subcaloric diet

diets for comparable periods of time. Even a differentiation between endocrine and simple obesity has been attempted on the basis of their behavior towards ketosis (16).

7 The influence of insulin on the non-diabetic ketosis. Thannhauser and Mezger (17), using regular insulin, were the first to observe a very small transitory decrease of the ketonuria in patients on low carbohydrate, low caloric diets. The 24-hour ketonuria, however, was not altered because the ketonuria increased after the patient recovered from hypoglycemia. Our results were obtained with protamine zinc insulin and show a very significant effect demonstrable on the 24-hour excretion as well as on the blood acetone level.

8 The glucose tolerance at the beginning of the starvation diet was normal in one and very slightly decreased in two patients. There was no relationship between glucose tolerance and degree of obesity. This factor is very frequently overlooked in the discussion of obesity as a predisposing condition for diabetes. No significant changes were observed after the use of the starvation diet. An improvement of the tolerance after weight reduction, as for instance Newburgh (18) has reported, could not be expected since our patients were still far above their ideal weight.

9 The diets, the caloric deficit, the ketogenic-antiketogenic ratio and the fat metabolism. The diet

supplied less than one-third of the basal caloric requirement of our patients and was very short of carbohydrates and fats and relatively rich in proteins, though the N minimum of 1 gm per kg was not covered. For an initial period the caloric deficit could be drawn from the glycogen reserves. It is, however, generally assumed that the available glycogen stores are exhausted after six or seven days and that the then remaining glycogen is not available for heat production. Whatever caloric needs exist after this period must be covered by the utilization of fats and to a smaller degree of proteins. The control of the N balance in our patients permits us to calculate the amount of calories derived from protein, the remaining caloric deficit must have been covered by body fat.

Our patients were not at basal conditions, since they were permitted to be out of bed throughout the day and to participate in minor exercises. Their caloric requirement can be assumed to have been 20 per cent above the basal calories and our further calculations are based on this figure. In spite of the constant diet, there was considerable variation in the caloric deficit since the BMR underwent rapid and marked changes. In Table II we have represented the calculations for one single day of each of the three patients. The ketogenic-antiketogenic ratio was calculated under the assumption that 60 per cent of protein and 10 per cent of fat are antiketogenic.

The table shows that for this particular day Patient L had a caloric deficit of 1719 calories. 40 calories were covered by 10 gm of body protein, the utilization of which was indicated by the excess excretion of 1.69 gm N. The remaining 1679 calories were derived from 187 gm of the patient's body fat. The 13 gm of

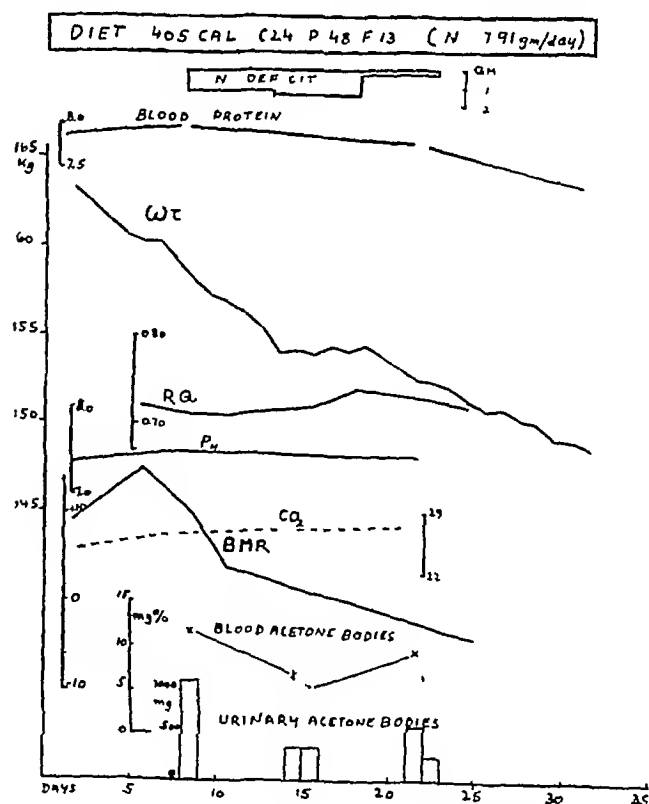


Fig 3 Patient J Ch, course of body weight (Wt), basal metabolic rate (BMR), respiratory quotient (RQ), CO_2 and pH in serum, blood proteins, blood acetone bodies and acetone-body excretion during 32 days on subcaloric diet (--- indicates insulin effect on blood acetone level)

exogenous dietary fat must be added to this figure in order to determine the total amount of fat burnt within 24 hours, which is 200 gm. Altogether, the necessary 2124 calories were derived from 30 gm carbohydrates, 42 gm exogenous and 10 gm endogenous protein and 13 gm exogenous and 187 gm endogenous fat. The ketogenic-antiketogenic ratio of the metabolic mixture was 2.48. This ratio is beyond Woodyatt's and Shaffer's ratios, according to which acidosis or at least marked ketosis should have occurred. Yet, there was no change in CO_2 and pH value of the patient's serum and the acetone excretion was only 1000 mg. Similar calculations show a ratio of 2.24 for Patient 2, whose acetone body excretion was within the normal range, and a ratio of 2.95 for Patient 3 who had a slightly increased acetone body excretion but also normal CO_2 and pH values in the serum. The total amounts of fat utilized within 24 hours were 150 gm and 261 gm in Patients 2 and 3.

How do these findings comply with Stadie's (4)

TABLE III

Ketogenic-antiketogenic ratios and the aketogenic fat utilization limit of Stadie (U_0) for the five obese patients of Mason (J Clin. Med., 4 93, 1927)

1	2	3		4	5
Case NR	Weight kg	K/A		Fat Utilized gm	U _o gm
		Highest Ratio	Last Ratio		
1	192.4	2.30	1.52	167.2	231
2	139.2	2.72	2.68	258.3	345
3	124.8	2.28	2.15	237.8	312
4	87.5	2.00	1.51	145.8	218
5	78.6	2.04	1.66	177.2	196

concept of fat metabolism and his maximal aketonuric fat utilization limit (U_0)? From in vitro experiments and analyses of the metabolism of acidotic diabetic patients he has concluded that "up to a certain level fat metabolism is complete and there is no ketosis. Beyond this level fat metabolism is incomplete and part of the fat catabolized is excreted in the form of ketobodies." U_0 , the level below which fat metabolism is aketonuric, was found to be around 25 gm per kg per day. Thus, the total amount of fat which can be utilized without the development of ketosis would vary with the variation of the body weights. Stadie has not stated whether his figure is based on the actual or the ideal weights. In obese persons these two values differ very much from each other. We have calculated the values of U_0 for our three patients on the basis of both the ideal and the actual weight (Table II, column 9). In one patient (S), the amount of fat actually utilized was smaller than both values, in the two others (L and Ch) it was between them. Since fat tissue is not mere ballast but participates in the body metabolism, the values of U_0 based on the actual weight seem more correct. Accepting these as the level of maximal aketonuric fat utilization we find that in all three of our patients this level was not reached. The lack of marked ketosis in our patients can be understood on the basis of this new theory.

If ketosis depends on both the total amount of utilized fat and the body weight, it also can be easily understood why obese persons have a very high aketonuric level, an experience which had caused considerable discussion in the earlier literature (16, 19, 20). Mason (21) published protocols of five obese patients who were kept on subcaloric diets over prolonged periods. None of the patients showed ketonuria at any time, in spite of high FA/G ratios. Table III represents the weight at the end of the observation period, the total amounts of fat utilized within 24 hours, Stadie's U_0 and the K/A ratios. Column 3 shows the highest ratio, as well as the ratio of the last observation day. It can be seen that the amount of fat actually used was lower than Stadie's aketonuric utilization limit for fat. McLellan, Spencer, Falk and DuBois (22) felt unable to explain why their obese subject did not show ketosis on an FA/G ratio of 2.4. This person (F. M.) weighed 153 kg, his diet contained 260 gm. of fat, but according to his weight his utilization limit for fat would be around 380 gm. Therefore, no ketosis occurred, in spite of the high ketogenic ratio.

In general, Stadie's concept also seems to explain satisfactorily why the ketosis in hunger and starvation is usually mild and stationary. If the utilization limit for fat is as high as 25 gm per kg per day, then 225 calories per kg per day could be supplied from the fat depots without the development of ketosis. The caloric requirement in undernutrition is low and will rarely exceed 25 calories per kg; it is partly covered by food intake. Consequently, the amount of body fat which is required to compensate for the caloric deficit rarely will reach the limit of complete fat utilization and thus ketonemia and ketonuria will not appear or be of mild degree, regardless of the ketogenic-antiketogenic ratio of the metabolic mixture. Ketosis, if present, will be stationary because of the rather constant amounts of fat and protein and of the carbohydrate derived from part of the protein and the glycerol fraction of the fat which are made available for the daily catabolism. This situation varies quantitatively only in complete starvation, where all of the caloric requirement must be covered by body substance, and where almost 100 per cent of the heat is derived from fat. And indeed the protocols of the famous starvation experiments of Zuntz (14), Brugsch (15) and Benedict (11), Folin and Denis (19) and others show that rather constant amounts of ketobodies were excreted within 24 hours regardless of the number of days of fasting. These experiments, however, reveal again the striking difference between ketosis in starvation and in diabetes. Besides the stationary ketosis in starvation in contradistinction to the progressive ketosis in diabetes there was in no instance a change of the acid base balance, even in those cases where the ketonuria was of a degree which in diabetes frequently is associated with acidosis. We know from the clinical experience of the pre-insulin era and especially from the hunger treatment of diabetes that "rather severe acidosis followed the period of complete starvation even in relatively mild cases of diabetes" (23). This discrepancy does not seem to be overcome by the new theory of ketogenesis.

Why does the starving diabetic organism oxidize so much more fat and develop a so much more severe ketosis than the normal organism in starvation? Their

caloric requirement does not differ and it should be covered by the same amount of fat if the fat oxidation is not affected by the impairment of the carbohydrate oxidation in diabetes. We feel with Woodyatt (24) that the problem starts again at this point. There is as yet no experimental evidence that the normal either of the diabetic organism is able to form carbohydrates out of fatty acids, and we must search for other explanations of this discrepancy. It may be that the inability to oxidize the small amounts of carbohydrates, which are normally derived from protein and glycerols, causes in diabetic ketosis the need for oxidation of ever increasing amounts of fat which necessarily is followed by an increase not only of ketonemia and ketonuria but also of the blood sugar. Furthermore, the lack of insulin may affect not only the carbohydrate metabolism but also the oxidation of the ketobodies which are produced beyond the limit of normal and complete utilization. The observations on the effect of insulin on the non-diabetic ketosis point in this direction. It may also be that Diagstedt's fat mobilizing hormone Lipociae is involved in this process. And, finally, the severe disturbances in water

and electrolyte distribution, which are always present in diabetic acidosis and which are not marked in starvation ketosis, may be most responsible for the different mechanisms of these two conditions (25).

The purpose of this study was to show that these problems still remain open in spite of the better understanding of the mechanism of ketosis.

SUMMARY

Observations on three obese persons on starvation diets are reported. Older findings about the rate of weight loss, reduction of the basal caloric requirement, the behavior of the respiratory quotient, the acid-base balance and the ketobody excretion have been confirmed. The effect of insulin on the non-diabetic ketosis has been demonstrated. The fat metabolism in starvation has been discussed and it has been found that Stadie's theory of a utilization limit for fat and a threshold for ketosis is compatible with observations on starvation ketosis. The still remaining differences between starvation ketosis and diabetic ketosis are emphasized.

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Treatment of Diabetes Mellitus Without Regard to Hyperglycemia and Glycosuria

By

HENRY J. JOHN, Lt. Col., M.C.
ATLANTA, GEORGIA

THE advocacy of the disregard of hyperglycemia and glycosuria in the treatment of diabetes mellitus has been voiced by some authors in the past few years.

The first questions that any physician who is treating a patient with diabetes mellitus must ask himself are: What is my aim? What must I do to justify my procedure, and what should be my goal? Is it only to keep a patient comfortable? Or is it simply to keep him free from reactions? These points are important but only in so far as they represent a rational basis in

the routine. The principle is the same as in finding a lump in the breast and keeping the patient comfortable by not doing anything about it, and giving her morphine to keep her comfortable when the pain becomes excruciating.

It is not difficult to keep a diabetic patient just comfortable, i.e., free from symptoms, little restriction of diet and little insulin will accomplish this. Neither is it difficult to keep him free from insulin reactions, small enough dosage below the point of hypoglycemia will accomplish this. But, having done this, have we discharged our obligations to the patient?

The ideal in the treatment of diabetes must be to restore the patient's physiology to as near normal as possible. Only then can we be sure that we have done our job well and that we need not fear any complications due to neglect. At the time of the first World War, Allen showed definitely the bad effects of hyperglycemia on a diabetic state which, by a continued hyperglycemia, becomes aggravated and a mild diabetic in time becomes a severe diabetic. That was in the period when we had no insulin to aid us and the hyperglycemia could be controlled only by the reduction of the diet. By such a reduction of the diet the patient's diabetic condition could be controlled. More recently Lukens and Dohan (2), by ingenious experimental work, demonstrated the detrimental influence of hyperglycemia on the islets of Langerhans and their gradual destruction through hyperglycemia.

weight in a patient on most any kind of routine, this is the least of all difficulties. It is equally easy to keep him symptom free for a time at least. Many patients are absolutely symptom free with a marked hyperglycemia. I have seen a woman past fifty years of age come to my office, not knowing she had diabetes, no symptoms of any kind, neither then nor any time previously, apparently in perfect health, with a blood sugar of 860 mg per cent which was confirmed on repeated examinations. So is the freedom from ketonuria easily achieved as long as the patient gets a reasonable diet and a certain dosage of insulin, even in the presence of a marked hyperglycemia as has been shown.

The absence of insulin reactions can be placed under two categories: (a) absence of insulin reactions with adequate control, and (b) absence of insulin reactions

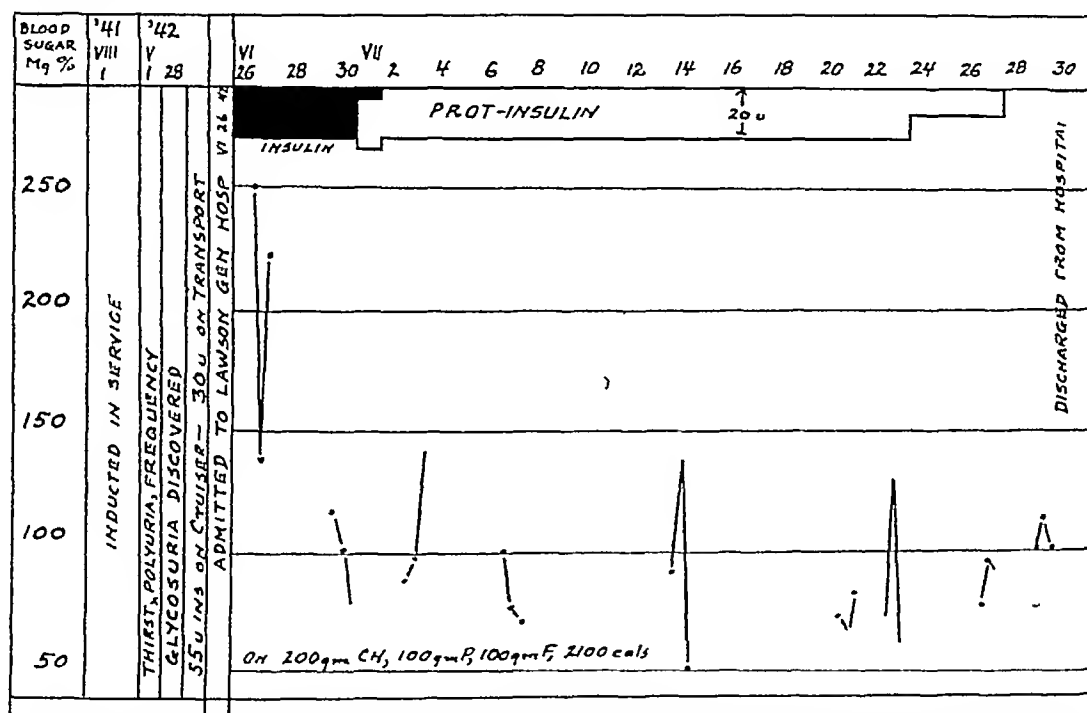


Chart I Progress of a young soldier with early diabetes mellitus. Note the control of hyperglycemia as evaluated by three blood sugars a day (one before each meal) which are connected by a line each day. When blood sugar is near the normal blood sugar level glycosuria is automatically eliminated.

These findings cannot be disregarded for they are the basic evidence of the evolution and the progression of diabetes through hyperglycemia. Thus in the therapy of diabetes, we come to this one criterion, namely, the abolition of hyperglycemia as far as possible.

However, without regard for the above facts, the following ideas in the treatment of diabetes mellitus are considered as ideal by one group of clinicians: (1) (a) one injection a day, (b) patient's weight at normal, (c) no symptoms, (d) freedom from ketonuria, (e) absence of insulin reactions, and (f) desirability of glycosuria.

Such points would be highly desirable were they not achieved at the patient's expense. One injection a day is certainly highly desirable and is achieved by most of us without the disregard of hyperglycemia which in turn means glycosuria. It is not hard to keep a steady

weight in the presence of inadequate control. The first is good, the second inadequate.

The desirability of glycosuria is completely opposed to all the progressive work done in the last 30 years, from Allen on. What does a heavy glycosuria mean? Simply a marked hyperglycemia for the most part of the 24 hours of each day. Such patients start out with a low blood sugar in the morning, but the noon, afternoon and night blood sugars are high. That means that for about 18 hours (75%) of the 24 hours there is a marked hyperglycemia which naturally is accompanied by a heavy excretion of sugar in the urine. The two go hand in hand and the actual quantity of sugar excreted depends on the height of renal threshold for sugar and the length of hyperglycemia. Diabetic patients of long standing have frequently a high renal

threshold so that even in the presence of a high hyperglycemia they may not excrete much sugar

There is a physiological hyperglycemia. Each individual, following a partaking of food has a hyperglycemia. This, however, is of short duration. From one to two hours after each meal the blood sugar is elevated. This rise is not marked, but may go as high as 200 mg per cent. Thus, a normal individual may carry a hyperglycemia for 6 hours each day (25 per cent of 24 hours). Here then, is our normal, physiological standard for the evaluation of the length of hyperglycemia permissible, an ideal for which we should strive. If by treatment we can keep a diabetic's hyperglycemia to 25 or 30 per cent out of the 24 hours we can feel that we have accomplished a desirable state. How to accomplish such an ideal is a matter of knowing how to use the insulin. That it can be accomplished is quite certain and most of the time it is accomplished with great ease. While this is especially true in early diabetics such as we have here in the Army, Chart I the same is true of the older and more severe diabetics, evidence of which I have given in previous publications. However, for the evaluation of the patient's condition, we need three blood sugars a day, one before each meal, to guide us as to the needed changes in insulin therapy. We may get along by the use of protamine insulin alone or we may need to add a little insulin to it, usually just temporarily, when we deal with a marked post-breakfast hyperglycemia resulting from the slow action of protamine insulin. Chart II-A is a record of the blood sugar levels and the protamine insulin dosage on a patient treated without regard for hyperglycemia (1). This data was taken on three separate days at intervals of one week. In Chart II-B, I have indicated possible changes in distribution of insulin that would convert the prolonged hyperglycemia to approximately normal blood sugar levels. (These changes indicate merely the principle, the actual detail may vary a bit depending on subsequent check-ups)

It is quite possible that the insulin could be given with the protamine insulin in one syringe which would enable us to use but one injection a day, but this point must always be determined by further examination of the blood sugars. If it works, then all is well, if not, then two separate injections must be instituted.

SUMMARY

1 In the treatment of diabetes mellitus one should strive not merely to keep a patient comfortable and free from insulin reactions but also to control his diabetic state, namely his hyperglycemia.

2 By the control of hyperglycemia, we automati-

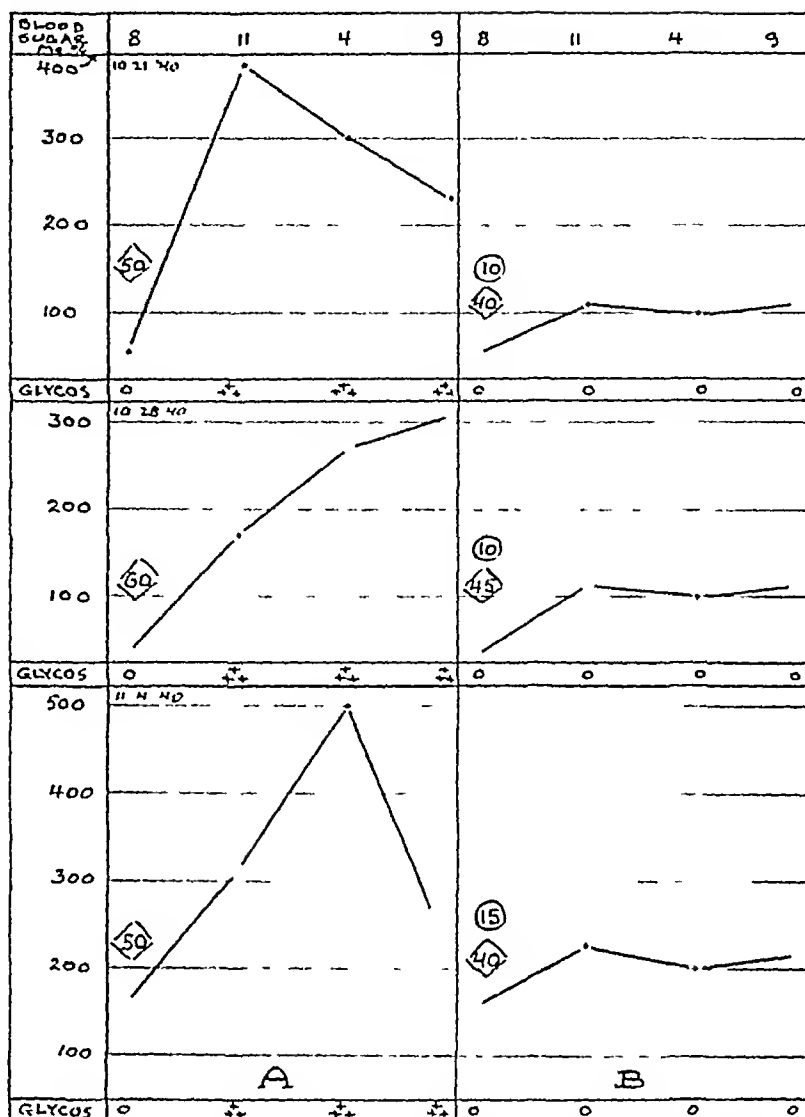


Chart II On the left (A) are drawn curves from the data as given by Tolstoi et al (1) on three separate days, one week apart and the dosage of protamine insulin indicated in diamonds. Note the marked hyperglycemia throughout the day in the presence of low fasting blood sugars. On the right (B) I indicated the remedy for the avoidance of such persistent hyperglycemia. Here the protamine insulin is indicated in diamonds and insulin in circles.

cally control all the other factors (glycosuria, ketonuria, weight, etc.)

3 Hyperglycemia has a deleterious effect on a diabetic state which thus becomes progressive and a more severe diabetic state results.

4 For the proper control of any diabetic condition, one needs extensive daily blood sugar studies which alone will enable one to distribute the insulin dosage wisely and adequately. Without such studies one has to work in the dark and do much guessing, and that usually at the patient's expense.

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Some Problems in the Diagnosis of Cancer of the Colon and Rectum*†

By

ABRAHAM TRASOFF, M.D., F.A.C.P.‡

and

DAVID H. GOODMAN, M.D.§

PHILADELPHIA, PENNSYLVANIA

WE have recently been confronted with two clinical problems in regard to cancer of the colon. One concerns a group of patients whose symptoms had no reference to the gastro-intestinal tract, and yet, after study, were found to be suffering from carcinoma of the colon. The other problem was presented by a group of patients, much larger in number, who had for varying periods of time complained of gastro-intestinal symptoms, some vague, and others more clearly defined. The latter patients had either been treated symptomatically, or as "functional" cases without gastro-intestinal studies. On admission to the hospital, they were found to have carcinoma of the colon, only too often in an inoperable state.

In spite of the fact that the literature on this subject is extensive (1, 2, 3, 4, 5, 6, 7, 8). These observations prompted us to review our cases of colon malignancy in the hope that some diagnostic criteria might be revealed which would enable us to make a diagnosis earlier in the course of the disease. Furthermore, we desire to emphasize the fact that of all cancer of the intestinal tract, cancer of the colon offers a particularly good prognosis, provided an early operation is performed. This is largely due to the fact that metastasis occurs late in the course of the disease and death is usually due to some complication such as obstruction or perforation.

The observations presented are based on 120 cases of cancer of colon and rectum definitely proven by adequate histologic study.

DISCUSSION

It is evident from our review, as has been pointed out before, that there is a difference in the clinical picture and symptomatology of carcinoma of the right half of the colon and that of the left half. Lesions of the right colon produce as their major symptoms abdominal pain, weight loss, dyspepsia and occasionally diarrhea. The presence of an anemia is frequent, and is of a severe grade in almost half of the cases. A mild leucocytosis is quite common.

The outstanding symptom of the left sided lesions is constipation, which is seen in at least 90% of all cases, although here too, diarrhea may occasionally be seen. Abdominal pain and melena are the next most frequently complained of symptoms, while weight loss is only half as common as it is in right sided lesions. A moderate anemia is present in the majority of cases but rarely reaches the severity seen in cecal lesions. The tendency to constipation found in the majority of

left sided lesions is due to the narrower caliber of the bowel in this location, together with more solid form of the feces and the tendency of growths here to be of the encircling and constrictive type. This is in contrast to growths of the right colon, particularly of the cecum, where the tumor, while larger, is typically fungating or ulcerative and does not usually produce obstructive symptoms because of the wider caliber of the bowel and more liquid character of the stool.

The presence of low-grade fever is very frequent in the clinical course of malignant growths. In the light of our findings it is probably due to complicating factors secondary to the malignant process such as perforations or abscess formation. It frequently indicates metastasis.

Growths of the rectum most commonly cause constipation and melena. Pain in the rectum or lower abdomen is frequently seen and a slight anemia is present in a high per cent of cases unless it is an early case. However, it is interesting that in no case was the hemoglobin less than 70%. The outstanding fact to be remembered about rectal malignancies is that practically all of them can be felt by simple digital examination. Even some of those high in the rectum can be felt if the patient is examined in the squatting position and while straining.

The "change of the bowel habit" so often stressed by various authors as diagnostic of cancer of the colon, while seen in the majority of our cases was not the earliest symptom in our series. From our study, the most frequent early symptom of cancer of the colon other than cancer of the rectum, is abdominal pain. The pain was generalized in many of the cases. In some it was localized to the area of growth. This was particularly true in right sided lesions. The pain was often ill defined and varied in intensity from a mere discomfort to a colicky type. The latter was particularly true in lesions of the left colon. It was persistent in many and remittent in others.

The diagnosis of cancer of the colon and rectum was made or suspected in 77% of our cases. In 49 colon studies by barium enema excluding the cases of cancer of the rectum, only 2 cases was a lesion not revealed by X-ray. In one other case an obstructive lesion was reported but interpreted as non-malignant in character by the roentgenologist. Thus it is seen that a study by barium enema is a highly accurate method of studying the colon for obstructive lesions. When it came to detecting lesions as low down as the rectum, however, the X-ray was not so infallible, for in 21 cases studied by barium enema 5 were reported as negative, and in three instances, while some slight irregularity was noted, malignancy was not suggested. Here, the proctosigmoidoscopic examination is all important, and

*From the Medical and Surgical Wards of the Mount Sinai Hospital Philadelphia, Pa.

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‡Chief of Medical Service No. 2.

§Clinical Assistant in the Department of Gastro-Enterology, Medical Service No. 2, Mount Sinai Hospital Philadelphia, Pa.
Submitted December 2, 1942.

in no case did it fail to reveal the lesion provided it was within the reach of the scope

The most difficult diagnostic problem we encountered was in a group of patients in whom the major symptoms and signs were those of the result of metastasis rather than pointing to the primary seat of the pathologic process. The citation of the symptoms of a few cases may be of interest. In one case it consisted of pain in the right sacro-iliac region treated for four months by his family physician for "sciatica." This symptom was most likely due to spine metastasis. In another case a painless swelling of the upper third of the left thigh was noticed a few weeks before hospitalization. It proved to be due to a metastatic infiltration of the lymph and venous channels of the upper thigh. A third patient complained of passage of feces in the urine which was the result of an entero-

120 cases of carcinoma of the colon and rectum

Cancer of the Colon—Number of cases 120 Males 68 Females 52
Age 24-85 (40% occurring in decade from 50-60)

	Summary by Location			
	Ascending 27 or 23%	Transverse 12 or 10%	Descending 37 or 30%	Rectum 44 or 37%
Duration of symptoms in months (before ad- mission)	5.2	5.1	4.4	7.1
Abdominal pain	90%	80%	80%	92% Rectal pain
Weight loss	66%	58%	33%	34%
Constipation	3%	9%	90%	60%
Diarrhea	15%	0	8%	7%
Melena	0	25%	22%	70%
Anorexia dyspepsia or nausea	33%	25%	0	0
Palpable mass	40%	40%	17%	91%
Moderate anemia (70 90% hb)	37%	50%	61%	78%
Severe anemia (below 70% hb)	40%	16%	8%	0
Leucocytosis (over 10 000)	48%	58%	14%	30%
X-ray diagnosis positive	94%	100%	95%	62%
Ca diagnosed or sus- pected clinically	85%	83%	70%	84%

vesical fistula at the site of the malignancy of the colon

We have been unable to find any criteria by which similar errors can be prevented. We can only conclude that one must be "colon-minded" when an obscure symptom or group of symptoms fail to be clarified by a careful study of the region involved. That too much time be not wasted before a complete and careful study of the colon is undertaken.

CONCLUSIONS

Although we have presented the usual symptoms and signs which are fairly typical of cancer in various parts of the colon, we feel that the diagnosis of cancer of the colon in early cases cannot be made on the basis of symptoms and physical examination alone, essential as these two factors are in making any diagnosis.

As we have shown, the X-ray and proctoscopic studies give us accurate findings in close to 98% of

our cases. We, therefore, feel that if we are ever to increase the number of cases of cancer of the colon that can be given early curative surgery, it is imperative that every patient, particularly those over 40 years of age, presenting persistent gastro-intestinal symptoms, should be subjected to careful X-ray and proctoscopic study. If these prove negative and the symptoms persist, the study should be repeated in 1-2 months. It is important to bear in mind that early symptoms of cancer may respond temporarily to medical treatment, and once the suspicion of malignancy is aroused it should not be lulled by the fact that the patient may feel better for a week or two on symptomatic treatment. Furthermore, the fact that a patient may have had some bowel symptoms for years should not allow the alert physician to immediately feel that the diagnosis is a minor or functional one. For a goodly number our cases had malignancies develop after being treated for some time for what well may have previously been a functional or benign ailment. This was especially seen in patients who had rectal bleeding which was found to be due to hemorrhoids.

One objection frequently offered to X-ray studies is that financial conditions often make such a study impossible. It is our opinion that such barriers can easily be overcome. The in-patient or out-patient department of any of our hospitals will, with the aid of the social service department, take care of this problem. It is only by this means that cancer of the colon can be diagnosed in its early stages and the patient immediately subjected to proper surgery which in good hands offers at least a five year cure in 30-50% of all cases.

SUMMARY

1 One hundred and twenty cases of cancer of the colon and rectum have been analyzed as to age, sex, symptomatology, laboratory studies and mortality.

2 Abdominal pain was found to be the most common early symptom of cancer of the colon. The differences in symptoms and findings of growths in various parts of the colon and rectum have been enumerated.

3 The problem of diagnosis in a group of obscure cases has been presented.

4 The difficulty in making a diagnosis of cancer of the bowel on the basis of the history and physical findings alone in early cases has been stressed.

5 A plea has been made for complete gastro-intestinal studies including X-ray and proctoscopy, in any patient presenting gastro-intestinal symptoms especially past middle life.

6 That carcinoma of the colon and rectum may be cured if operated upon early has been emphasized.

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Ketosis in Health and Disease

By

JOSEPH H. BARACH, M.D.
PITTSBURGH, PENNSYLVANIA

ANYONE evaluating the progress of medicine for the year 1942, should credit this year with a generally increased knowledge and a better understanding of the origin and meaning of ketosis. While it is true that the physiologist, the biochemist and the experimental pathologist have long known of the occurrence of acetoneuria in health, workers in clinical medicine have looked upon it as a manifestation of disease. The clinician subconsciously has a wholesome respect for ketosis, even a fear of it, because of what he sees in diabetic coma whose former mortality rate of more than 60 per cent has in recent times and in good hands been lowered to somewhere near 5 per cent.

Acetonuria and its clinical effects were studied by Stadelman as early as 1885, and by Gerhart, Engel and Von Jacksh in the same year. The work of Minkowski and Magnus Levy in 1889, Rosenfield and Hirschfeld (1895), Geelmuyden (1897), Naunyn (1898) and Von Noorden (1907) (1), is largely responsible for the knowledge which forms the basis of our present-day conceptions of ketosis and acidosis in health and disease.

KETONES IN THE ABSENCE OF DISEASE

It has been known since the work of J. Muller (1898) Von Jacksh, Engel and others (1) that approximately 10 to 30 mgm of acetone may be recovered from the urine and 30 to 80 mgm per day may be eliminated by the lungs of healthy individuals. When more than a physiological amount of acetone is present and the underlying error in metabolism that is responsible for it is allowed to continue, ketones will accumulate to a level at which diacetic acid and beta-hydroxybutyric acid can be detected in the body fluids.

THE ORIGIN OF KETOSIS

Under ideal normal conditions, the balanced diet of man in the northern temperate zone obtains approximately 65 per cent of its calories from carbohydrate, 15 to 20 per cent from protein and 15 to 20 per cent of its calories from fat. From this it is apparent that the metabolism of normal man in a physiological state is geared to oxidize and utilize each of the three food substances in these proportions. Acetone bodies are not demonstrable in urine of normal individuals living on a normal diet, by our ordinary methods of testing. When however for one reason or another the carbohydrate content of the diet is inadequate or when in the absence of insulin carbohydrate is lost to the metabolism and the total or nearly total nutritional requirement is met by the breaking down of fat and protein then the acetone bodies which are break down products of fat metabolism make their appearance in abnormal amounts.

The acetone bodies to which we refer here are diacetic acid, beta-hydroxybutyric acid and acetone.

The terms "acetone bodies" and "ketone bodies" are used here in their usual clinical sense. Of the three substances usually grouped under the term "ketone bodies," namely acetoacetic acid, beta-hydroxybutyric acid and acetone, said Soskin and Levine, "The second is not a ketone, while the third represents merely a break-down product of its more physiologically significant precursors" (1A). The appearance of acetone in the blood, urine or expired air means that diacetic acid is or was present and it always bespeaks a pre-existing carbohydrate insufficiency.

Magnus Levy in 1910 (2), postulated that beta-hydroxybutyric acid undergoes oxidation into diacetic acid and from that acetone is formed. Acetone can be made out of acetic acid by splitting off carbon dioxide. As seen in the urine of diabetic patients the ketones ordinarily are found in the following sequence, acetone, diacetic acid and beta-hydroxybutyric acid. Beta-hydroxybutyric acid chemically is butyric acid plus one atom of oxygen. Injected into rabbits, beta-hydroxybutyric acid will not cause coma but diacetic acid does. Von Noorden claimed that beta-hydroxybutyric acid is the primary substance and that it is oxidized into diacetic acid from which acetone is formed. Jowett and Quastel claim that diacetic acid is the first substance to be formed and that hydroxybutyric acid plus one atom of oxygen forms beta-hydroxybutyric acid. Beta-hydroxybutyric acid plus two molecules of acetic acid forms diacetic acid and when diacetic acid loses carbon dioxide acetone is formed.

Whatever be the exact sequence of the various steps in the formation of ketones, the clinically important thing is that they are produced in the liver and they are eliminated continually by the way of the respiratory and urinary tracts. So long as ketones are eliminated as rapidly as they are produced, there is no accumulation and there are no toxic effects. When, for one reason or another, elimination lags, and there is an excess of ketones in the blood and in the tissues, ketosis and intoxication follow and the clinical picture of coma may sooner or later make its appearance.

KETONES: NORMAL OR ABNORMAL PRODUCTS?

It is at this point that real progress in our knowledge of ketosis has been achieved during the past few years. The experimental studies of Quastel and Whentley, Snapper and Grunbaum, Edison, Stadie and the latest work of Soskin and of Mirsky and their associates (4, 5, 6, 7, 8, 9, 10) all indicate that the acetone bodies, which in the past were considered abnormal products of incomplete oxidation of fats, are in reality normal end products in the normal metabolism of fats within the liver. It has also been shown that acetone bodies are utilized freely by the muscles in health and in diabetes.

The experimental physiologist of today is coming to the conclusion that acetone bodies primarily are not

pathologic This brings us to the question, "What does clinical experience in health and disease have to offer that will confirm or deny the correctness of this latest interpretation of the nature of acetone bodies and what is their clinical significance?"

KETOSIS FOLLOWING RAPID DEPLETION OF GLYCOGEN STORES IN HEALTH

During muscular activity, the glycogen which has been stored in the body is utilized freely, in proportion to the strenuousness of the effort and its duration. Within the muscles, glycogen is broken down into lactic acid and utilized as such. Or when lactic acid is carried to the liver, it is converted into glycogen and then distributed for use. It has been known for a long time that following muscular exertion, small amounts of lactic acid may be found in the urine.

Since 1907, very few studies have been made or recorded concerning the presence of acetone bodies in the urine as a result of carbohydrate depletion following muscular exertion. Courtice and Douglas, in 1936, (11), observed that prolonged muscular effort causes a change in the respiratory quotient and the appearance of acetone in the urine as indicated by a positive Rothera's test. Mills, in 1938, (12), also found acetone in a man who walked 10 miles at the rate of $4\frac{1}{2}$ miles per hour. Courtice, Douglas and Priestley (13) in 1939, noted a lowering of respiratory quotient, a prolonged glucose tolerance test and a positive acetone reaction after prolonged exertion. It is therefore of interest and importance at this time to re-state my findings in a study on the physiological and pathological effects of severe muscular exertion presented before the American Physiological Society in 1910 (14).

Observations were made in a group of 55 young men who trained for and ran the Marathon race. This inordinate effort consisted of running the classical distance of 24.85 miles in the shortest possible time. The winner of the race finished in $3\frac{3}{4}$ hours while the last to finish within the required time came in at the end of 4 hours. It is evident that the metabolism of these young men during that run was stepped up to a very high level, and glycogen utilization was at its maximum. While, in fasting, the body normally contains enough glycogen to carry on for an entire day, we see here that the available glycogen can, under certain conditions, be used up in 3 hours or less.

The average loss in body weight in these young men was 3.1 pounds and the maximum loss was 8.5 pounds in 4 hours. The body temperature varied from normal to 104 degrees, the winner of the race finished with a temperature of 102.6 degrees Fahrenheit. Of the 55 contestants who started, only 19 finished within the allotted time of 4 hours. The urine of all of these was examined before the race and immediately thereafter. In the urines of the 19 who finished, not one of the specimens contained acetone or diacetic acid before the race, but all of them contained acetone bodies after the race. Diacetic acid was found either in considerable or large amounts, acetone was present in all, and beta-hydroxybutyric acid was present in the ones tested for it. The Gerhaid test for lactic acid was positive. Another interesting finding was, that half of these specimens, those which contained the largest amounts of diacetic acid, also contained considerable albumin and "showers of casts," the kind of thing that is seen in diabetic coma.

The significance of these observations lies in the fact that a group of healthy young men, who had been living normally and were at the height of physical efficiency, exhausted their stored glycogen within a period of 3 to 4 hours so completely, that their immediate energy requirements could be met only out of fat and protein reserves. The time element of 3 to 4 hours presents a rather interesting phenomenon and no doubt it is governed by a basic law in human physiology. This three hour period is seen in the rise and fall of the blood sugar level, as depicted in the glucose tolerance curves, and it is seen in the post-prandial blood sugar curve three times daily.

It is evident that a short period of maximum work can deplete the glycogen stores in the body of a whole day's supply within three hours, instead of 24 hours. There were other evidences of glucose exhaustion aside from the appearance of acetone bodies, which indicate carbohydrate deficiency. As these young men finished the race, they presented a well defined clinical syndrome. There was extreme nervousness and excitement, there was cold sweat, rapid pulse, facial pallor, delirium and a certain number of them lapsed into unconsciousness which continued in one case for more than 12 hours. In the light of what we know now, it was the clinical picture which accompanies hypoglycemia, it was the picture of insulin reaction, or the so-called insulin shock.

In a series of observations on Marathon runners by Levine, Gordon and Denick (15) in 1924, it was demonstrated that hypoglycemia and its clinical syndrome was well marked in a considerable proportion of their cases. They also found a rise in the NPN and uric acid, and a lowering of the blood carbon dioxide, these findings coinciding completely with what is usually present in ketosis. In this connection I wish to quote the recent discussion on "Physiology of Work" by Ivy of Chicago (16). "Maximal work is defined as that which yields an average metabolic rate of 8 to 20 times the basal metabolic rate of 1600 to 1800 calories. Maximal work is frequently performed in sports or in the laboratory. Except in emergencies few persons will work at such an intensity as to produce a hyper-pyrexia and a critically low blood sugar. Heavy muscular work does not increase the requirement for protein above the usual 70-100 grams but it does increase the requirement for fat and carbohydrate."

In this instance the maximal work, and I should say it was truly maximal, led to physical exhaustion within 3 to 4 hours. It is readily seen that the usual amount of stored glycogen, 300 gram, whose caloric value is 1200 calories, would be used up in considerably less than 4 hours in one whose temperature had risen from the normal to 102 or 104 degrees Fahrenheit, and in one who had lost from 3 to 8.5 pounds of weight.

• If we are to summarize these observations we must note that a healthy young man can subject himself to a maximum work period in which he will exhaust his glycogen stores, and draw excessively on protein and fats to meet his caloric needs. When that occurs his fat metabolism will exceed the physiological bounds, and the liver will release excessive amounts of ketones. At the end of his effort he will present a clinical syndrome characteristic of hypoglycemia such as is seen in insulin reaction. His blood will show hypoglycemia, increased NPN and a lowering of the blood CO_2 .

His urine may show acetone, diacetic acid or beta-oxibutyric acid and give a positive reaction for lactic acid. The urine may also show albumin and in those with the larger amounts of ketonuria showers of casts characteristic of ketosis, may be found. The entire clinical and laboratory picture is one of ketosis. The dividing line here between the physiological and the pathological is a narrow one and there is much evidence to substantiate the viewpoint that acetone bodies are normal products in normal metabolism making their appearance when disproportionate amounts of fat are being metabolized.

KETOSIS IN DISEASES OTHER THAN DIABETES

There are a number of other conditions in which ketosis occurs from time to time. In this group we find cases of self-imposed fasting and unavoidable starvation or inanition, as seen in certain mental and nervous states. Ketosis occurs in infections, in fevers, intoxications, in disease of the gastro-intestinal tract, in cyclic vomiting after anesthesia and during labor in pregnancy. Ketosis has been quite common in the post-operative period of thyroidectomy. It was my experience a number of years ago when pre-operative care was not as well managed as it is today, to have found 66 per cent of a series of thyroidectomies showing ketonuria during the first three post-operative days. Ketosis is not infrequently found in neglected cases brought to the hospital as surgical emergencies in whom a quick restoration of glucose balance is imperative.

Whatever the origin, whether it is because the patient fails to ingest carbohydrate, or loses it, or is unable to utilize it after he does take it, the effect and its consequences are always the same.

This brings us to the point where we may allocate the ketones to their proper place in the metabolism. Ketones are products of normal fat metabolism within the liver, and they are normal so long as they exist within the bounds of what is physiological. Uric acid is a normal constituent of the blood and tissues but when it accumulates to a point at which it produces gout, then the existence of uric acid is abnormal. Cholesterol is a normal constituent of blood and bile but not to a level at which it forms calculi or when it calcifies the wall of a gall bladder. Mucous is normal in the colon but not in such amounts as the found in mucous colitis. Water is the normal solvent for urinary constituents but not in the quantities that

occur in diabetes insipidus. Glucose is normal but not hyperglucosemia as seen in diabetes mellitus. If there is one place in the description of diabetes in which the term over-production is really applicable, it is in this connection. Production of acetone bodies in the liver is normal but over production of acetone bodies creates abnormal states such as ketosis and coma.

KETOSIS IN DIABETES

Up to this point we have considered the finding of ketones or acetoneuria in those who are free of disease and in those who are ill of diseases other than diabetes. In both instances we can associate the cause of this with inadequate supply of carbohydrate for the immediate needs of the metabolism. The next question is whether the *modus operandi* of ketosis is the same in diabetes as it is in non-diabetic states and on this point the following clinical observations have a direct bearing.

At the end of the pre-insulin era, we made a study of the frequency with which ketonuria was found in 100 consecutive cases of diabetes. The patients comprising this series in the first half of 1923 had not yet been given insulin, and they were on a high fat and low carbohydrate diet as was the practice of that day. As shown in Table I, 43 per cent of these patients at some time or another during that year, showed acetone or diacetic acid in the urine. In the second half of 1923 we were embarked on the use of larger amounts of carbohydrate both in patients receiving insulin and in those not receiving insulin and we were moving in the direction of a normal diet (17). We began trading off one gram of fat for two grams of carbohydrate and pushing that to the limit of tolerance. Our plan was to 'give the largest amount of carbohydrate that the patient could tolerate without causing glycosuria and hyperglycemia.'

With our patients on that regimen, we learned that 40 per cent of diabetics could take a diet generous in carbohydrate and low in fat, and we also learned that they could take a good maintenance diet without the use of insulin. For us that ended the use of high fat diets and its 33 per cent incidence of ketonuria. In 1932 we again reviewed the incidence of ketosis in diabetics. The patients included in that survey were on a low fat and higher carbohydrate diet. Our findings then revealed that ketonuria occurred in only 4 per cent of the cases. The net result of this was that

TABLE I
Ketosis incidence
1923 to 1932

Year	Number of Specimens	Number of Patients	Diet			Ketone	Source
			Carbohydrate	Fat	Insulin		
1923		100	Low	High	None	43	Private
1924	600	100	High	Low	None	3	Private
1925	227	100	High	Low	None	2	Private
1926 to 1928	2304	65	High	Low	Yes	60	Diabetics
1929 to 1932	2416	117	High	Low	Yes	4	Private

with the low fat and higher carbohydrate diet, we succeeded in reducing the incidence of ketonuria in our patients during that year from 43 in every hundred to three per hundred patients.

In 1934, we made a survey of a group of patients under continuous treatment. This time we summarized the incidence of ketonuria in the specimens at 836 consecutive visits, our findings revealed that ketonuria occurred in 2 per cent of the cases. A recent survey covering the years 1937 to 1942 reveals that in 10,168 patients visits we find an incidence of the occurrence of acetone in 4%. This is on the relatively low fat and higher carbohydrate diet. It is also interesting to note that the incidence of acetoneuria was no higher in the 6386 dispensary visits than it was in the 1148 private visits.

The one logical conclusion from all this is that in the diabetic, ketosis makes its appearance when there is an inadequate carbohydrate metabolism and a proportionately excessive amount of fat metabolism, and these accumulated evidences indicate that the underlying cause of ketosis is the same, whether it occurs in health or in disease, in non-diabetics or in diabetics. In diabetes the absence of insulin leads to loss of sugar to the metabolism, insulin being the check which keeps sugar production and utilization within bounds. In diabetes the unavailability of carbohydrates leads to excess fat metabolism and over-production of acetone bodies. This is what the physiologist of today is proving in the experimental laboratory, and this is what we see daily in the medical clinic when we analyze our material correctly.

TREATMENT OF KETOSIS AND COMA IN DIABETES

One of the distressing emergencies that falls to the practitioner of medicine is the treatment of a case of diabetic coma. The physician knows that the longer the patient remains in coma, the sooner he will die, and he also knows that the earlier adequate treatment is instituted, the sooner the patient will be restored. It is not a simple matter, in fact it is very difficult or almost impossible, to properly evaluate the gravity of a patient's condition from the history and physical examination alone. One feels very much at sea in ordering treatment for a case of diabetic coma without preliminary laboratory reports. What we aim to do in the treatment of a case of diabetic coma is to restore the chemistry of the patient to the normal, and that can be best accomplished after knowing the ex-

tent to which the patient's chemistry is already altered.

A most useful aid in the correct evaluation of the severity of a case of diabetic coma will be found in the tabulation of the so-called prognostic factors. This plan originally proposed by Rabinowitch of Montreal (18), has been constructed into a table with some modifications as shown in Table II. It will be noted that, whether the case is to be considered mild, moderate, severe or profound depends upon the age of the patient, duration of the comatose state, the level of the blood pressure, the level of the blood CO₂, the urea nitrogen or non-protein nitrogen, the presence or absence of infection, of complications, and the degree of unconsciousness. When each of these factors is checked on the chart as outlined for an individual case, a very satisfactory evaluation of the case is attained.

Accompanying Table II is Table III. This second table serves as a starting point for treatment of the patient. The patient evaluated as a mild case is given 100 to 150 units, the moderate case is given 200-300, a severe case is given 300 to 400 units and a case in profound coma is given 400 units or more of insulin. Our experience with this usage and dosage of insulin as outlined, has been entirely satisfactory. Up to the present time, the last 25 out of 26 cases of diabetic coma, appraised and treated in this fashion, have recovered. It will be noted that half of the total dose of insulin is in the form of protamine-zinc insulin, and that has been entirely satisfactory in our hands. It will also be seen that for every unit of insulin the patient is given 2 grams of glucose and with that we give plenty of fluids in the 24 hours. We believe that the additional glucose increases glycogen, and tends to replace the need for further oxidation of fats, thereby reducing the formation of acetone bodies. There are two schools of thought concerning the use of sodium bicarbonate intravenously, we leave that optional depending upon the degree of apnea. Where the breathing is decidedly irregular or too shallow, a moderate dose of sodium bicarbonate 10 to 20 grams intravenously, in our experience, has at times seemed distinctly beneficial. The bicarbonate restores base, affects oliguria favorably and this amount, as far as we have seen, has not precipitated alkalosis. It has also been our custom for some time to administer oxygen when the breathing is bad, certainly no harm but good can come of its use. We are not unmindful of the fact that some men of large experience treat coma without additional glucose.

TABLE II
Diagnostic factors in diabetic coma

Severity Index	Mild	Moderate	Severe	Profound	Profound
1 Age	15	30	45	60	70
2 Duration	12	24	36	48	60
3 Blood pressure—Diastolic	80	60	60-50	50-40	40
4 Blood sugar	300	500	800	1000	1000+
5 Plasma CO ₂ —vol %	20	15	10	5	3
6 Blood urea nitrogen or non protein nitrogen	20	30	40	50	60
	40	60	80	100	120
7 Infection			++	+++	++++
8 Complications			Coffee-ground vomitus	C V Ren	C V Ren
			Unconscious but responds	++	+++
9 Degree of unconsciousness	Drowsy	Semi-conscious	Unconscious but responds	Completely unconscious	Completely unconscious

To evaluate seriousness of a case of diabetic coma checkmark each severity index factor (1 to 8)

Column containing maximum number of checks indicates degree of coma and insulin dosage

In addition to above evaluate glycosuria leukocytosis diacidic acid acetone, body temperature fever rapid pulse respiration albuminuria showers of casts.

TABLE III
Treatment of diabetic coma
Insulin—Glucose—Salt only*

Degree of Coma	Total Insulin Units	Percentage Subcutaneous	Percentage Intravenous	Percentage Subcutaneous	Glucose Per Hour	Glucose Per Day	Fluids cc. Per Day
Mild	100 to 150	50 to 75	25 to 50	25 to 50	10 to 15 grams	30 to 50	Give 250 cc. for every 100 cc. of patient's body weight. 100 cc. every 2 hours. 100 cc. every 2 hours. 100 cc. every 2 hours.
Moderate	20 to 30	10 to 25	30 to 50	75 to 90	10 to 20 grams	20 to 40	
Severe	100 to 200	10 to 25	75	75	5 grams	10 to 20	
Profound	100 to 200	5	10	90	5 grams	10 to 20	

- * After admission, take blood for analysis. Give the three doses of insulin at once. Insulin for subcutaneous use should be diluted into 1 or 4 portions and injected into different sites for better absorption. Glucose is given hourly as per schedule by mouth, through tube or vein. Glucose by mouth may be given as pure glucose or one of our special Glucose Syringes mixed with water or tea and flavored with lemon juice. Glucose liquid, cream and essential vitamin when necessary. Give 100 cc. insulin in each alternate glucose administration. * Important. The routine is for an average patient of average body size. Extraordinary cases require individual adjustment.

and without sodium bicarbonate with excellent results. What we can say is that the method of treatment outlined here because of the added elements of certainty and because of its therapeutic success has served us well.

SUMMARY AND CONCLUSION

The increased knowledge and the better understanding that has come to us during the past few years out of the laboratory of the experimental physiologist and biochemist is when the liver is depleted of a normal supply of glycogen it will proceed immediately to break down fats and proteins for energy requirement of the organism. Once begun, this process goes on to a degree that produces increasing amounts of ketones. This can occur in health within a period of 3 hours

as in our Marathon runners and it occurs in disease, the pathologic physiology is the same, regardless of the duration or circumstance of its development. When formation of ketones exceeds the rate at which they can be eliminated, accumulation in the tissues will follow and ketosis and coma will result. This coma can be overcome by giving the patient glucose, insulin and water. Glucose as material for the manufacture of glycogen and the restoration of a normal chemistry within the liver, insulin to make this conversion possible and water to facilitate the exchange. While this is in the process of restoration ketones are being eliminated and oxidized, the excessive breaking down of fat ceases and a normal chemistry is restored.

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The Postural Treatment of Biliary Colic[†] (Its relation to the prevention of acute cholecystitis)

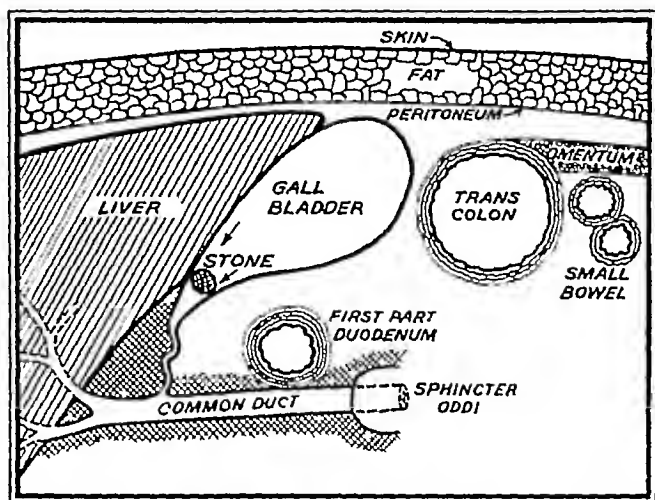
By

DEAN MACDONALD M.D. F.A.C.S.
ST. CATHERINES, ONTARIO, CANADA

THE relationship of a gall bladder calculus to acute cholecystitis is well known but seldom appreciated. Acute inflammatory changes in the gall bladder are, in practically every instance, the direct result of calculus obstruction of the cystic duct.* It is the precise

possession as well as the immediate causal factor. This condition must, in every instance, be recognized as serious and potentially dangerous and contrary to the belief in some quarters it requires a maximum of clinical acumen and surgical judgment if the best end results are to be obtained. There are few other abdominal conditions whose immediate and future pathologic as well as immediate and future prognosis de-

*See Article Cholecystitis, 4th Ser. L. 1931.
†All other cases are recognized for their comparative commonness.
Summit, November 17, 1931.



PATIENT LYING ON BACK

Fig 1 This represents a patient lying in bed in the usual position. It is obvious that the force of gravity, as well as the increased intra-vesical pressure which results from excessive mucosal secretion, both tend to force the stone further into the duct. The calculus, of course, often dislodges itself, but this happening is due to good luck more than to good management.

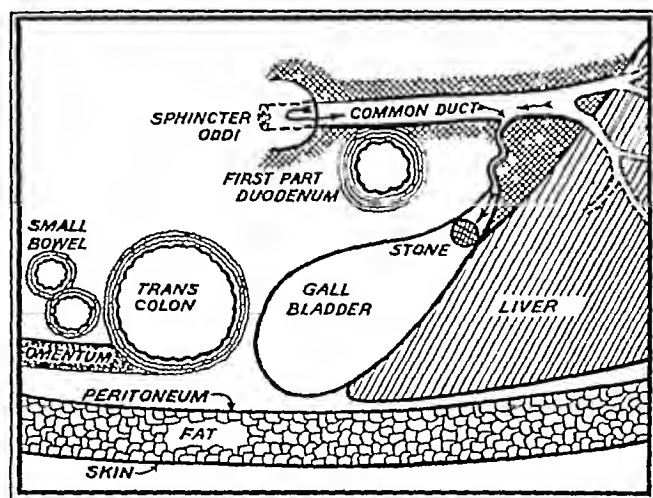
depends as much upon an *early* and wise decision regarding the course of treatment. This is usually the responsibility of the general practitioner. It is therefore in order to discuss the possible control of any etiological factor of clinical acute cholecystitis. For all practical purposes the principal and primary etiological factor is cystic duct obstruction by calculus, i.e. biliary colic. This must be considered in its pathological sense and not as a pain requiring opiates. It is an obstruction in a hollow tube and may be as serious, if not relieved, as other obstructive lesions in hollow tubes, e.g. a strangulated hernia or a vascular embolism. The satisfactory control of this obstruction, *while it is still early and while it is still the only factor to combat*, will reduce the incidence of acute cholecystitis. If this control is not exercised, changes may occur which "lock" the stone in place and which may produce the resultant and serious condition known pathologically (and accurately) as "acute obstructive cholecystitis." This locking mechanism consists, early in the process, of edema and congestion, but if it progresses it may produce vascular thrombosis, local and generalized necrosis, gangrene, suppuration and perforation—alone or in combination (Fig 3). Therefore, the prevention of calculus impaction really means the prevention of these complications. When the calculus has become immersed by edema and congestion of the mucous membrane, it cannot be dislocated by any active effort less than surgery and from this point on, if surgery is not done and the obstruction remains, the pathology is progressive. The pathology of such cases varies within wide limits and the end-results also vary, but everyone is a potential fatality. Hence every calculus colic (not functional) demands the profound respect of the attending physician, notwithstanding the many reports in the literature that conservative treatment of acute gall bladder inflammation is satisfactory and even successful.

This paper suggests a new method of treatment of biliary colic which may prove to be of value in the prevention of acute cholecystitis. Although it has been

used in only six cases, it has been successful in all. Even in view of this very small number of patients it is thought that the treatment deserves a serious and criticizing consideration. To be successful the patient must be seen, and treatment must be instituted early, i.e. early from the pathological viewpoint. Successful therapy is usually based on prevention. Indeed this is a fundamental prerequisite. In this instance the prevention of calculus impaction is the aim of treatment. It is therefore the general practitioner who must be "on the alert." It should be mentioned, also, that every biliary colic, provided that the presence of stones can be proven, is a positive indication for surgical treatment, at the proper time. This means that the treatment of calculus disease, acute or chronic, must never be expectant. Such treatment implies that the pathology, including the calculi, will "clear up and maybe disappear." This attitude is not warranted from a pathological viewpoint.

It is probable that the medical (conservative or expectant) treatment of pathological acute cholecystitis does not control the final outcome of any particular attack. However, the factors which determine whether an attack of colic (obstruction) will subside or progress are still absent during the early mechanical obstructive process, and are therefore, at this stage, at least partially controllable by medical methods. If the obstruction persists, and the resulting changes occur, these controllable factors gradually disappear until, by the time clinical acute cholecystitis is established, they are medically uncontrollable (Fig 3).

There are three principal factors concerned with every case of acute obstructive cholecystitis, namely, (1) obstruction, (2) interference with the blood supply, (3) infection. It is obvious that medical treatment does not determine the type or extent of infection present, (even though drug therapy may influence the progress of such infection). It is likewise obvious that conservative treatment is not likely to alter vascular changes, or prevent further changes occurring. It



PATIENT LYING ON STOMACH

Fig 2 When a patient is lying on the abdomen it is obvious that the force of gravity is a help in displacing the calculus. In addition to this postural treatment, choleretic drugs are administered and the resulting increased flow of bile is directed against the stone from the direction which is most likely to displace it. Such pressure is further increased when the resistance of the sphincter of Oddi is raised by the administration of morphine.

does not do so in other obstructive lesions of hollow abdominal tubes, as, for example mesenteric vascular accidents, obstructive bowel lesions, acute appendiceal obstruction, etc.—nor does it likely do so in relation to the obstructive lesion in cystic duct obstruction. In other words, if these acute intra-abdominal obstructive conditions resolve and subside, they are persuaded to do so by some factors outside our control. Thus it is probable that at the very outset of acute pathological—as contrasted to clinical—cholecystitis the die has been cast, and that the changes, either for better or worse are going to run their course regardless of heat, morphine fluids, etc. Indeed, we all believe this and so we watch the temperature, and pulse, and the abdomen, carefully to see if we can tell whether the pathology is regressing or progressing and consequently whether surgery should be done. *We watch it—we don't change it or alter its course.* If it changes—it changes itself (Mother Nature and the law of averages are on our side—and how much they help us!) Hence we have no control over the interference

calculus, with the aid of gravity, will have a much greater chance of being dislodged from the narrowing cystic duct, and it will more likely fall to the most dependent part of the viscus. This chance of dislodgement is increased if the relaxing and relieving action of antispasmodics, vasodilators and sedatives are made use of, and here is applied to the abdomen (reflex).

To increase the probability of the stone being dislodged a pressure head of bile is directed against it from the ductal side in the following way. Morphine (gr 1/6) is administered to close the sphincter of Oddi, or at least increase its resistance to intraductal pressure, and the intraductal pressure is then increased by the giving of choleretic drugs. This increased flow of bile under greater pressure because of the increased resistance of the sphincter of Oddi, is thus directed into the cystic duct and against the calculus from the direction which will most likely dislodge it. This procedure will not, of course, always displace the calculus but it is maintained that the inci-

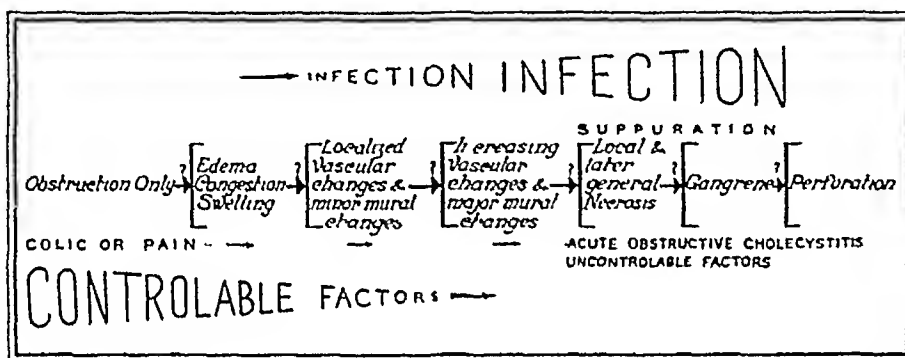


Fig 3 This chart schematically represents the basic idea of the early postural treatment of biliary colic. The controllable factors decrease as complications are added to the original simple obstruction, and as infection is added, they gradually disappear and finally become the uncontrollable factors which increase in direct proportion to the advance of the infection and the progress of the pathology. It is obvious that the sooner active efforts are made to dislodge the stone, the greater is the chance of preventing the succeeding steps which complicate the original simple obstruction, and in many instances lead to clinical acute cholecystitis (pathological acute obstructive cholecystitis).

with the blood vascular changes on the infection—but—and this bears a repetition—we do have some control over the obstructive agent early in its life i.e., while it is still movable.

This fundamental fact seems to have long been neglected. It is reasonable to believe that, in a certain number of cases, such a movable and mechanical obstruction can be controlled—early—by (1) a change in the action of gravity on the stone and by (2), a change in the pressure mechanism of the factor or factors holding it in place.

Fig 1 represents semi-diagrammatically a patient lying on the back, in bed, with a calculus resting in the mouth of the cystic duct. In this position the force of gravity and the continually increasing intravesical pressure, which is produced as a result of excessive mucosal secretion, both tend to shove the stone further into the cystic duct. If the stone is wedged in this position, obstruction will be permanent and acute pathology is almost inevitable. This mechanical obstruction is partially overcome, or at least it is not persuaded to remain and increase, if the patient lies on the abdomen (Fig 2). In this latter position the

dence of clinical acute obstructive cholecystitis will be decreased in direct proportion to the earliness with which this treatment is started in the course of biliary colic or suggestive pain. Indeed it is not improbable that the relief of colic or biliary pain which follows the administration of morphine is due to this mechanism in a minor way.

A summary of this preventative treatment is as follows and is instituted at the earliest possible moment.

- 1 The patient must lie flat on the abdomen.
- 2 Morphine is administered in small doses (gr 1/6)—(so that it may be repeated)—to increase the resistance of the sphincter of Oddi. This may produce a loss of pain but must not lull the physician into a sense of security.
- 3 Antispasmodics and vasodilators are given in large doses to relax any contractile mechanism in the cystic duct—(examples: amyl nitrite inhalation, nitroglycerine gr 1-100 under tongue, neurotransentin tab IV by mouth, tincture belladonna M XXX by mouth, atropine gr 1/50 by hypodermic, trasentin ampule II by hypodermic).

4 Sedatives are used to produce both mental and physical rest

5 Choleletic drugs are used to increase flow of bile—(examples Decholin tab 3 q1h for two doses, Bilon cap 3 q1h for two doses, Ketachol tab 3 q1h for two doses)

6 Heat to abdomen

7 Surgery if necessary—and when prepared—for the prevention of empyema, necrosis, gangrene, or perforation

In addition the following factors are of benefit

1 Rest and quiet

2 Protection of the liver

3 Plenty of fluids if necessary

4 Gastric lavage with heated fluids

It is understood that treatment includes careful and watchful attention. The patient should be prepared for operation if the colic does not soon subside. *Good conservative treatment is also good pre-operative treatment but that is all it should be.* Surgery may take the form of the two-stage procedure advocated by the author

Biliary Constipation

By

HARRY GAUSS, M.D.*

DENVER, COLORADO

THE mechanism of constipation is intimately related to the problem of water balance of the colon. Much has been written on the causes of constipation, as well as its varieties, symptoms, complications and treatment, yet the subject of water balance of the colon has received scant attention. This is so perhaps because little is known about it. Yet the control of water balance is the basic factor which operates in the production of constipation.

We have become accustomed to taking water for granted. Water is the common solvent for all the body fluids. Water is the common vehicle for practically all the body chemical functions. Water functions in secretion, absorption, excretion, osmosis and a host of other chemical activities. Water regulates the body temperature, water flushes the bowel, it removes waste matter from the kidneys, it lubricates the mucous membranes, it functions in the phenomena of sight, smell and taste, etc. Yet water itself must be controlled in each of these activities in some particular manner.

In the case of the general tissue water of the body, much knowledge has been gathered as to the manner in which it operates.

Water is ingested normally through the mouth into the digestive tract, although there are other routes of entrance into the body, as intravenous, rectal, subcutaneous, etc. However the normal manner of entrance is ingestion into the digestive tract. After ingestion, absorption takes place to a slight degree from the stomach, largely from the small intestine and somewhat from the large intestine. Water is absorbed as a solution whose osmotic pressure is nearly equal to that of the blood. If the ingested food solution is sufficiently dilute, it is absorbed directly, but if the ingested food solution is concentrated above that of the blood, then it is diluted by water which is secreted by the gut in sufficient amounts to bring the osmotic pressure down to a point suitable for absorption. Water is thus secreted by the glands of the mouth, stomach and intestine into the gut in amounts varying from two to ten liters a day (Adolph (1)). However, after the final absorption of the digested foods has taken place, some of the water which remains is re-

sorbed by the colon. In this manner the colon acts like the condenser of a steam engine as pointed out by Alvarez (2). After its absorption into the body, water is controlled by (1) the osmotic pressure of the blood proteins, (2) the hydrostatic pressure of the capillaries and small blood vessels and (3) certain other factors of lesser importance as the osmotic pressure of tissue cells, turgor pressure, etc.

Water does not just float around the body tissues in any haphazard manner. Its behavior is regulated by definite physical-chemical factors. The osmotic pressure exerted by the blood serum is equal to 30 mm of mercury, while the hydrostatic pressure in the arteries is 120 mm, in the capillaries it is 25 mm and in the veins it is 6.7 mm (Dubois (3)).

Water is excreted from the body in the urine, expired air, sweat, insensible cutaneous loss, and feces. Many factors influence the amount of water which remains in the body, as exercise, food ingestion, salt ingestion, protein absorption, pyloric obstruction, vitamin level, kidney disorders, dehydration, hemorrhage, nutritional disorders, etc.

However it is the water content of the bowel which is of special interest to us at this time. Since the stool is approximately eighty per cent water, it is evident that the water balance of the colon is extremely important in the mechanism of constipation.

The factors which control the water balance of the colon are partly known and partly conjectural. On the known side are: water is ingested as food or drink, it is absorbed sparingly from the stomach, freely from the small intestine and somewhat from the colon, it is secreted by the mucosa into the gut to aid in the process of digestion and assimilation and reabsorbed in the colon which acts as a condenser. On the speculative side are the factors which determine the amount of water which remains in the colon to form the bulk for the stool.

Early clinicians have long recognized that there is a marked difference in the behavior of colons in respect to their absorption of water, that some colons have a tendency to absorb water to the point where the stools become hard and dry. They spoke of these as greedy colons.

In the case of tissue water, the principal factors

*Department of Medicine University of Colorado

which operate to hold water in the body are (1) the osmotic pressure exerted by the blood proteins and (2) the hydrostatic pressure from the blood vessels. In the case of colon water, the factors which operate to hold the water to form the bulk for stools is speculative. However certain observations suggest that the bile plays an important role in controlling the colon water in a manner somewhat similar to the osmotic pressure exerted by blood proteins on tissue water. Let us examine the facts.

It is the function of the colon to receive the end products of digestion from the small bowel, to complete digestion and remove the absorbable water, returning it to the general circulation. The colon thus receives the semifluid chyme from the small intestine, completes the absorption of the nutriment and water, thus converting a semifluid chyme to a putty like mass which is the ideal state for the stool. If the job is too well done, the stool becomes hard and dry forming a constipated stool, and the colon which does this was called the greedy colon by our medical grandfathers. It must be evident that there must be some substance which determines the amount of residual water in the stool.

Let us consider the behavior of the bile in the bowel. We assume that from 600 to 900 cc of bile are secreted daily. Actually we do not know just how much is secreted under basic conditions, but these are the generally accepted figures. If the bile exerts an osmotic pressure on the water tending to hold it in place, then a reduction of the amount of bile would lessen the osmotic pressure on the water content and so favor dehydration of the stool. This conforms to the clinical observation that those patients who suffer with biliary or hepatic disease in whom there is reason to believe that there exists a decrease in the flow of bile are generally constipated.

Unfortunately our knowledge of the behavior of the liver and biliary tree in disease leaves much to be desired. Our functional tests on liver behavior are far from satisfactory, certainly we have no test for measuring the amount of bile secreted into the intestine under basic conditions. There are numerous disorders of the liver and biliary tree which probably reduce the secretion or flow of bile. These will be followed by a reduction in the osmotic pressure exerted on the water in the colon resulting in the formation of dry stools.

Besides the osmotic pressure which bile exerts on the water, it has other functions. Horrall (4) believes that bile has the particular characteristic of stimulating bowel activity, that bile and bile salts entering the intestinal canal through their natural channels have a stimulating effect on the motility of the small intestine, that bile is necessary for normal movements of the intestinal tract.

Constipation is the rule in patients with jaundice. Now jaundice is a dramatic episode which occurs in certain diseases of the liver and biliary tree. For every case of jaundice, there must be very many more cases of lesser disease or obstruction, insufficient in themselves to cause jaundice, yet sufficient to reduce the secretion or flow of bile. In short there are numerous disorders of the liver and biliary tree which interfere with the formation or free flow of bile into the intestine, thereby causing constipation. We designate this as the biliary type of constipation.

Biliary constipation is apt to occur in persons with cholelithiasis, cholecystitis, gall bladder dyspepsia, biliousness and other disorders. It must be realized that long before gall stones are formed in a gall bladder there must exist a condition of stasis or stagnation which prepares the way for gall stone formation. These pre-gall stones states are probably associated with a reduced flow of bile.

The recognition of biliary constipation as a distinct type is important because the treatment depends on the diagnosis which is practically specific.

Biliary constipation occurs in middle aged persons of sedentary habits with biliary or hepatic disease, which may be either organic or functional. It occurs in both sexes, but it is of greater frequency in women. It occurs in the fifth, sixth and seventh decades of life. It results from a diminished flow of bile resulting in a diminished osmotic pressure exerted on the water content of the colon as well as a reduction of the normal stimulus to peristalsis.

The symptoms are a mixture of gall bladder dyspepsia and the spastic colon syndromes. Thus there will occur the "fair, fat, forty and flatulence" symptoms of gall bladder dyspepsia combined with the complaint of dry hard stools unsatisfactory in character, of infrequent occurrence of the spastic colon syndrome. Other symptoms are tenderness under one or both hypochondria, epigastric distress, vague abdominal pains, coated tongue, offensive breath, mental and physical sluggishness, anorexia, abdominal consciousness. Certain foods are apt to disagree as cabbage, cauliflower, radishes, cucumber, raw apples, cantaloupes, peppers, onions, etc. The person is listless, sleeps poorly, often lacks the power to concentrate on his work, is a bad listener and a poor companion.

Physical examination shows a person whose general nutrition is slightly below par. He may have a sallow complexion, a coated tongue, an offensive breath. There may be some tenderness under the costal margins, a spastic palpable tender descending colon.

The Ewald test meal is not specific, although the tendency is for a hypoacidity or achylia. X-ray will show a spastic irritable colon, while the gall bladder shadows are extremely variable. Sometimes the gall bladder will show stones, sometimes deformities, sometimes delayed filling and emptying time, sometimes it will not visualize at all, and sometimes it is of normal configuration with normal filling and emptying time. The stool is reduced in size, amount and caliber, it is hard, dry, fragmented or sheep dung in type. The color is apt to be normal. Occasionally the color may be light or even clay colored. When this occurs the diagnosis is suggested.

The treatment is fairly simple and almost specific. Since the whole conception of biliary constipation is based on the principle of reduced bile flow, the basis of treatment is to increase the flow of bile, and the only satisfactory manner of doing this is to give either whole bile or bile salts. It accomplishes nothing to give bland diets, vitamins, sedatives and antispasmodics or other procedures if the bile salts are omitted. Bile is the only satisfactory way to stimulate the flow of bile. Bile salts act as cholagogues and choleretics. Cholagogues increase the flow of bile while choleretics increase the secretion of bile. Bile and bile salts are specifically indicated in the treatment of biliary constipation.

Unfortunately there is no standardized dose for bile preparations. Often the dose has to be adjusted to the individual. We usually start with a safe initial dose and increase the amount according to the person's tolerance. If the dose is too large, it will produce diarrhea and cramps. In this case it is necessary to reduce the amount of the drug. The writer has found the following forms of bile salt therapy useful: (1) Bilron (Lilly) which is a form of iron bile salts. The initial dose is one capsule three times a day. (2) Kapseals Desicol (Parke Davis) which is dried soluble whole bile. The initial dose is one capsule three times a day. (3) Katochol (Seale) which is a form of oxidized bile acids. The initial dose is one tablet three times daily. With the increased flow of bile, the stools become larger, bulkier, well formed and moist. Defecation becomes satisfactory to the patient leaving him with a sense of well being instead of the feeling of oppression which so often occurs following defecation in spastic colon. The dose of bile salts must be adjusted to the person. Sometimes it must be increased above the initial dose, sometimes reduced.

Additional treatment consists of a bland diet in which the writer includes whole wheat cereals and bread because of the high Vitamin B complex content, sometimes a normal diet with the irritating foods as onion, cabbage, cauliflower, radishes, peppers, fried and greasy foods, etc., are removed. Sedatives, antispasmodics are useful so is Vitamin B complex. Rest and relaxation are helpful.

The following case report illustrates a typical instance of biliary constipation and its management.

CASE REPORT

D. F. C., a druggist of 45 years, had been constipated for many years. He complained of unsatisfactory stools. He might go several days without having an evacuation. His stools were small in size, fragmented and unsatisfactory. He had tried many remedies in an attempt to correct his constipation. He had tried mineral oil, mineral oil combinations with agar, various types of colloid gels, psylla seed preparations, karaya gum preparations, etc.

He also complained of anorexia, insomnia, coated tongue, belching, flatulence, abdominal consciousness, epigastric fullness after meals. He had an intolerance for cabbage, cauliflower, onions, raw apples, cucumber, fried and greasy foods. On several occasions he has passed clay colored stools. He had had numerous attacks of biliousness, but has never been jaundiced. Otherwise there is nothing of importance in his history.

Physical examination shows a fairly well nourished white male 45 years old, 5 feet, 9 inches in height, weighing 178 pounds. His temperature is 98.2, his pulse is 82, his respiration is 16, his blood pressure is 158/65. His eyes, throat, ears, hearing and lungs are within normal limits. His abdomen shows a spastic palpable and tender descending colon. The reflexes are present, equal and somewhat diminished. The blood and urine are within normal limits. The Ewald test meal shows a free acid of 10 and a total acidity of 25. The E. K. G. is normal.

X-ray of the gall bladder shows it to be of normal

configuration without stones, it concentrates the dye well. Three hours after a fatty meal it shows delayed emptying time. The stomach is normal. The cap fills well. The colon shows a marked spasticity of the left half of the transverse and the entire descending segments.

Diagnosis Biliary Constipation, Spastic Colon, Gall Bladder Dyspepsia.

The patient was placed on a bland diet and given Bilron capsules (Lilly) one capsule three times a day, also he was encouraged to make the most of his opportunities for rest and relaxation. He reported a week later to state that he was much improved, free of his epigastric oppression and was enjoying normal bulky moist stools for the first time in years. Since then he has reported from time to time for a period of two years. He states that as long as he takes the bile salts he is free of constipation and most of his distressing symptoms. However, whenever he becomes preoccupied and forgets to take his bile salts, the symptoms quickly return. He has gone through this cycle several times with the same result. Bile salts have relieved his constipation and given him normal stools when other forms of treatment have failed to give him relief.

SUMMARY

1 The mechanism of constipation is intimately related to the problem of water balance of the colon.

2 The factors which control the water balance of the colon are undetermined, however it is reasonable to suppose that the bile plays an important role in its control.

3 Diseases of the liver and biliary tract in which there is reason to believe that there is a reduced formation or flow of bile are usually characterized by biliary constipation.

4 Biliary constipation occurs commonly in middle aged persons of sedentary habits in whom there is present some form of biliary or hepatic disease either functional or organic.

5 The symptoms are a mixture of those resulting from gall bladder dyspepsia syndrome and the spastic colon syndrome.

6 The diagnosis is made from clinical observations.

7 The treatment is fairly simple and practically specific. It consists in giving whole bile or bile salts. Supplementary treatment consists in a bland diet including whole grain cereals, antispasmodics, sedatives and rest.

8 Biliary constipation is a common type of constipation in middle aged persons.

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the tumor mass becomes elongated and protrudes with defecation. The pile is still somewhat elastic and retracts into the lumen after defecation is completed. In this stage there is apt to be less bleeding and the annoying symptom is the protrusion with each bowel movement.

As the fibrous tissue of the pile becomes excessive the tumor loses its elasticity, the sphincter muscle loses its tonicity from continued pressure, there is marked protrusion with each bowel movement, which must be replaced digitally, and the mass protrudes on the slightest exertion such as walking, coughing or bending, and it may then continuously hang out of a patulous anus. At this stage abrasions of the protruding mass may occasion massive hemorrhages, sometimes sufficient to produce marked anemia. Strangulation is present when the blood supply is interfered with by the edema of incarceration, producing superficial gangrenous areas. In this stage thrombosis of some of the internal hemorrhoidal veins is frequent. This occurs as the result of infection of the mass and is exquisitely painful, completely incapacitating the patient.

Mrs. M. F., No. , housewife, age 52 years. For 15 years she has had fullness about the anus and protrusions after defecation. There was very little bleeding until the past year, but now there is bleeding and pain accompanying each defecation. She has lost 50 pounds in the last 5 years and has grown very nervous. She has occasional pyrosis and flatulence. Bowels are irregular, appetite good. Frequent dysuria. Menarche at age of 13, menopause at 51 years.

Blood morphology	Hemoglobin	84%
	RBC	4,760,000
	WBC	7,650
	Color index	89
	Eosinophiles	2
	Neutrophiles	60
	Lymphocytes	36
	Monocytes	4

This patient was submitted to an ordinary hemoidectomy but had a stormy convalescence and required considerable sedative medication. After leaving the hospital she complained of pain around the anus and "gas" pains. Mineral oil $\frac{1}{2}$ ounce morning and evening was given. Because her blood picture was practically normal though somewhat hypochromic she was given (1) Liver extract—1 cc intramuscular injections every 3 days, (2) one-half ounce of Elixir Thiamine chloride with iron in a glass of fruit juice sipped slowly during each meal. Within a month her RBC had risen to 5,245,000, her color index to 1.06, her weight increased 7 pounds and she commented on how well and energetic she felt. The liver, iron and B₁ were continued until she had regained 20 pounds. In this case it is our opinion that the psychosis and fatigue syndrome was due to the prolonged loss of blood and the patient's health could be restored only by an energetic course of hemopoietic therapy.

CARCINOMA OF THE COLON AND RECTUM

It is well known that anemia invariably accompanies neoplasms of the bowel. This occurs so routinely that loss of weight, loss of appetite, or pallor of the skin in an adult leads the clinician to suspect a malignant process. Because this anemia may appear in patients with only a small growth or recent history and with-

out evidence of metastasis it has been thought that the malignant process either elaborates a product capable of bone marrow inhibition, or in its growth utilizes a product necessary for red cell production.

Although the exact mechanism of the anemia of malignancy is unsettled, there does seem to occur degrees of anemia that are entirely out of proportion to the extent of the malignant growth. The anemia usually seen in such states is definitely hypochromic. The red cells are reduced in number, the hemoglobin reduced to a greater extent and the color index below one. The red cells are microcytic or they may be normal in size, occasionally when there is metastasis to the liver the cells may be macrocytic.

The frequent dribbling and sometimes massive hemorrhages from cancer of the colon or rectum are always a source of worry to the physician. The diagnosis of carcinoma of the terminal portion of the large bowel is best made by feeling and seeing the growth, but any disease which produces an ulcer, a mass, a stricture, or which is characterized by the passage of blood or pus, must be considered in the differential diagnosis of cancer. Other lesions to be so considered are diverticulitis, ulcerative colitis, volvulus and hemorrhoids.

In the early stages of malignant disease a diarrhea is frequently mentioned. It is usually mild but on rare occasions it may occur with forcible spontaneity and later in the disease this urgency amounts to a degree of incontinence. The formed stools are likely to be blood streaked when the tumors occur in the left half of the colon or in the rectum, whereas if the growth is in the right colon gross blood is rarely seen until late. At any rate the passage of blood in any patient, no matter how well he otherwise seems, with or without mucus or pus, should always be investigated by digital or rectosigmoidoscopic examination.

The hemolytic anemia of malignant disease is not well understood. Profound changes occur in the blood of all cancer patients and are usually more marked in growths of the cecum and right colon than in those of the descending colon or rectum. Sometimes marked changes occur as the only outstanding symptom. Too often in advanced cancer patients these hematopoietic disturbances are described as cachexia, without any effort being made to relieve them. Waugh (1) divides the causative factors into primary and secondary groups. The primary causes are those due directly to the cancer cells themselves or the chemical substances arising from them, that is their metabolic or excretory products.

Secondary products are those which result from the effects of the tumor on other organs and viscera of the body. These latter changes are much more common and the mechanism of their production is more obvious. They explain many of the changes frequently attributed to cachexia.

All malignancies of the digestive tract, as they reach the ulcerative stage, and persistently lose blood, produce a typical posthemorrhagic or hemolytic anemia. If the bleeding is small in amount or occult the actual blood loss may not be appreciated until a grave anemia results. Achlohydria also frequently accompanies malignancies of the bowel and may lead to an erroneous diagnosis of pernicious anemia. The blood morphology of the anemia of malignancy is, however, quite different from that of pernicious anemia. In

cancer the blood cells are small with low hemoglobin concentration and if nucleated red cells are present they are of the normoblastic or macroblastic type, in contrast to the megaloblastic forms of pernicious anemia. Moreover, there is not the reduction of myeloid white cells nor the thrombocytopenia and bilirubinemia of pernicious anemia.

The blood picture of post-hemorrhagic anemia is not always present because many of these patients have been on reduced fluid intake, or suffer from diarrhea and an anhydremia results, due to its quantitative reduction, and the blood morphology is that of a pseudopolythemia with a high refraction index of the blood plasma. Anoxemia from poor aeration of the blood is another cause of the increase in red blood cells which may reach 16 million count.

A very definite leukocytosis is frequently present, particularly the neutrophiles and monocytes. The neutrophiles show more or less immaturity and frequently a comparatively large number of myelocytes. The eosinophiles may not show any change and the lymphocytes are reduced. Many of these changes in the white cells are explainable on the basis of the inflammatory changes present in the tumor. If however a massive hemorrhage has occurred the leukocytes may, in part at least, be due to associated leukopoietic activity of the bone marrow.

A hemorrhagic diathesis may result when metastatic masses in the liver produce obstruction to the bile ducts and jaundice.

If metastasis extends to the bones nucleated red cells may be found and also myelocytes and myeloblasts.

Prolapse of the sigmoid into the rectum occurs occasionally in obstinately constipated individuals who strain at stool. Congestion resulting from pinching of the bowel may cause bleeding. Usually the bowel is slowly retracted and drawn upward through the constriction and the condition goes undiagnosed. If, however, discomfort and tenesmus persists for a long period after defecation the diagnosis may be established by sigmoidoscopy and the condition studied during the act of straining. Prolapsion of the rectum protruding through the anus occurs much more frequently and is so obvious that both patient and physician recognize the condition immediately.

3. Colon lesions

In the absence of malignancy, bleeding from the colon is usually due to ulcerative colitis of the idiopathic, amebic or bacillary type, polyposis of the colon, tuberculous ulceration of the bowel, diverticulitis, intussusception, parasites, trauma or actinomycosis.

CHRONIC ULCERATIVE COLITIS

The history of chronic ulcerative colitis is always suggestive of the malady. Frequent bloody, mucopurulent rectal discharges mixed with varying amounts of feces is the usual complaint. The diarrhea, borborygmus and tenesmus begin insidiously and increase gradually. In the meanwhile the patient loses weight and appetite and the facies shows the distress. In the acute fulminating cases there is a septic type of fever, many bloody, purulent rectal discharges, night sweats and herpes labialis. A peculiar, gray pallor is common, and varying degrees of anemia come on.

The stools are soft, semiliquid to liquid, bloody, mucopurulent masses, usually composed predominantly

of pus but at times mostly of blood and containing blood clots as well as blood intimately mixed with the stool and discharge. With each evacuation a considerable amount of blood is lost, sometimes a cupful. Some evacuations are almost entirely of blood and the patient can be kept alive only by repeated blood transfusions.

A distinctive blood picture is noted in most cases of chronic ulcerative colitis. There is present a hemoglobin deficiency with an almost normal leukocyte count and a greatly increased sedimentation rate of the red blood cells.

Proctoscopic findings

In the early stage of the disease, there is seen hyperemia, then edema followed by or in conjunction with, diffuse, military abscesses or pin-point ulcers. The rectum and sigmoid often appear granular and glazed with bleeding. Large shaggy ulcers caused by coalescence of the military ones occur in the more severe stage of the disease and the islets of mucosa between reveal the typical signs of granular, easily bleeding mucous membrane.

In advanced cases the X-ray of the barium filled colon shows the region narrowed, shortened and lacking the normal haustral marks.

Amebic colitis has the characteristic diarrheal stool of other dysenteries but with only a small quantity of mucus and pus. The proctoscopic appearance is characteristic. The mucosa of the rectum and sigmoid is studded with ulcers which are quite superficial, varying in size from 2 to 8 mm. They are oval or slit like, and covered with a fleck of mucus, which, when removed with a cotton applicator leaves a bleeding surface. The mucosa between the ulcers appears normal and does not bleed when manipulated with the applicator. Material removed from the ulcer should be examined at once microscopically for the endameba histolytica. The barium enema is of no value in amebic colitis as it shows but an irritable colon.

POLYPOSIS OF THE COLON

The symptoms of polyposis of the colon depend on the amount of involvement of the bowel, the degree of obstruction or ulceration caused by it, and the secondary manifestations such as intoxication and anemia. The cardinal symptoms are pain in the abdomen and rectal discharges of blood and mucus. Most of these small tumors are adenomas, some are papillomas. They rarely cause an alarming hemorrhage. As a rule, blood will be noted on one side of the fecal mass. In the diffuse polyposis associated with chronic ulcerative colitis bleeding may be quite profuse.

INTESTINAL TUBERCULOSIS

The tumor of hyperplastic tuberculosis is usually in the cecum. Pain, intermittent, sharp and colicky in character coming on after eating and especially the evening meal is usually the first sign. Diarrhea appears later, as a rule, and occurs in a large proportion of cases, being periodic and alternating with normal bowel movements or constipation. Hemorrhage is rare but some gross and microscopic blood is usually present. There is progressive loss of weight and anemia but less than occurs in cancer.

Diverticulosis of the colon only rarely causes gross bleeding. When free blood is seen it is from an ulcer.

ating diverticula. At that time intense inflammation surrounds the entire area and involves the peritoneum (diverticulitis) producing a palpable inflammatory mass, and obstruction difficult to differentiate from carcinoma.

Thrombosis of a mesenteric vein may cause a massive loss of blood into the colon but is a rare accident.

Intussusception is rare in adults though it occurs more frequently in infants or young children under 2 years of age, and is in them to be suspected whenever blood is passed from the rectum.

An acute hemorrhagic colitis of toxic origin may result from the therapeutic use of mercurial or arsenical

preparations, especially after intravenous administration. It may also follow ingestion of these chemicals or of mineral acids or carbonic acid ingested for suicidal or homicidal intent. Proctoscopically the bowel mucosa is a deep red color, freely oozing blood and bleeding readily after even gentle use of a cotton applicator.

Injury by foreign bodies swallowed or introduced into the rectum may give rise to gross bleeding. A crushing injury to the abdomen may be followed by intraintestinal hemorrhage.

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Metastatic Melanotic Sarcoma to the Ileum Causing Intussusception

By

JOHN ROBERTS PHILLIPS, M.D.
HOUSTON, TEXAS

TUMORS of the small intestine, either of primary or of secondary origin are not common. The presence of a metastatic tumor in the mucous membrane of the small intestine is unusual. The case that I wish to report is one of a melanotic sarcoma primary in a mole on the face, which metastasized to the lymph nodes of the chest, to the ileum and to the thigh. The metastatic growth in the ileum presented itself as a cauliflower polypoid type of growth, which caused an intussusception. At post-mortem examination we felt that the patient was probably suffering from two primary malignancies from the gross examination because the polypoid tumor in the ileum appeared to be malignant and there was glandular involvement in the mesentery. However, on microscopic study it was found that the tumor was a melanotic sarcoma and that the character of the cells were identical with those of the primary growth.

REPORT OF CASE

The patient, a white female, age 38, consulted me first on February 27, 1941, because of an ulcerated area in front of the right ear, about the size of a nickel. This started as an ulceration on a mole, which had been present all of her life. Prior to coming to me she had had two X-ray treatments over this area and had had the lesion partially destroyed by electric needle. Due to the fact that the lesion would not heal she sought further advice. I felt that the process was a malignant one and examination of the glands of the neck revealed them to be enlarged. There was so much infection in the lesion I was unable to tell whether these glands were inflammatory or malignant. The entire sloughing area was removed with the diathermy loop and the area thoroughly cauterized, leaving a destroyed area about four centimeters in diameter. Within a week the glands in the neck were explored and found to be involved in a malignant process. The pathological diagnosis was melanotic sarcoma, so that a radical dissection of the glands of the neck, removing the submental, submaxillary and the deep cervical glands was carried out on the right side. The patient made an uneventful recovery. In about five weeks the destroyed area on the face had healed and the patient felt quite well. Her general examination at that time, including an X-ray of

her chest, was negative. Due to the fact that she had had numerous attacks of biliary colic an X-ray was made and showed that she had gall stones. It was not felt advisable that anything should be done about this at that particular time. On January 8, 1942, or almost a year after the radical excision of the glands in the neck with the destruction of the tumor, the patient presented herself to me again because of a nodule that had formed in the mid-thigh along the course of the saphenous vein. It was about the size of a lemon and was rather fixed. It had a bluish discoloration to it, very much like there was a large hematoma present. Complete examination at that time revealed the head and neck to be negative. The scars were in good condition and there was no evidence of any recurrence in the glands of the neck. X-ray of the chest was negative. Her pelvic and rectal examination was negative, as was the abdominal examination. There was a tumor mass in the middle third of the right thigh along the course of the saphenous vein. I felt as though it could be a hematoma, but advised its removal. This was done January 9, 1942, and upon wide excision, staying wide of the tumor, it was found that it could be completely enucleated. It was entirely in the soft tissues and upon microscopic study it was found to be a melanotic sarcoma of the same character as the primary lesion. The patient made an uneventful recovery from this, but soon thereafter began to show rather marked anemia so that repeated transfusions were necessary in order to keep her blood up. It was felt that she probably also had metastasis to her liver, although nothing could be felt by abdominal examination. There was no evidence of any blood loss and X-ray examination of her stomach and colon revealed no evidence of tumor or ulceration. Her anemia was really very hard to control and she would have to be transfused, using 500 cc's of blood about once a week. Throughout this time, however, she never showed any evidence of blood loss and her general condition continued good, there never being any evidence of any cachexia or weight loss.

On June 23, 1942, she began to have rather severe upper abdominal pain without any distention and without vomiting. Her bowels continued to move normally. The pain was quite severe, requiring hypodermics for relief so that we felt that the pain was due to the gall bladder disease with stones. Due to the increase in severity and the difficulty in controlling the pain, on August 29, 1942, exploration of the abdomen was carried out, at which time

cholecystectomy was done for sub acute cholecystitis with stones. There were no stones in the common duct. Examination of the stomach was negative, as was examination of the liver. Examination of the mesentery revealed large glands which were quite definitely metastatic. There was no distention of the small bowel. Although a complete examination of the small bowel was not carried out, apparently at that time there was no definite obstruction and it was felt that the gall bladder was the cause of the patient's complaints. Following removal of the gall bladder, the patient was able to go home within ten days and continued to do well for a month, at the end of which time, she began having recurrent attacks of abdominal pain, intermittent in character, associated with nausea, vomiting and distention, so that we were then sure that she was suffering from an obstruction and by this time we were able to palpate a mass in the mid lower abdomen and could feel it by vagina. We felt as though the metastatic glands had progressed to the point where they were causing obstruction to the intestine. At one time the obstruction almost became complete, but by Wangenstein suction enemas and intravenous fluids, we were able to relieve the obstruction so that she was able to return to her home within a few days.

For the last month of her life she was kept fairly comfortable with light diet and remained in her home up until the day before her death, at which time she was readmitted to the hospital with a definite obstruction and evidence of peritonitis. The mass in the abdomen had increased materially in size.

Post-mortem examination revealed no evidence of recurrence in the face or in the glands of the neck. There was a melanotic sarcoma in the hilar node of the right lung about the size of a lemon. The lungs were not involved in any metastatic processes. The stomach and duodenum was negative. A section of the liver revealed no metastasis. The biliary tract was perfectly normal. The gall bladder had been removed. In the lower right quadrant there was a rather large metastatic gland mass. The terminal ileum was rather markedly dilated and there was an area of intussusception. On opening the ileum it was

found that there was a pedunculated polypoid cauliflower tumor in the terminal ileum which had caused an intussusception. The tumor mass measured two and one half centimeters in diameter and was attached by a rather long pedicle. Grossly we felt that the patient was suffering from a second primary malignancy, but upon section of this tumor it was found that it was a melanotic sarcoma presenting itself as a polypoid growth. The glands were involved in the same melanotic process.

DISCUSSION

We had not been able to diagnose this tumor in the ileum before death. The X-rays had been negative except immediately prior to her death, there was evidence of rather marked intestinal obstruction. X-rays of the stomach and colon, as stated, had been entirely negative, and we were more or less at a loss to know just why the patient suffered from such a profound recurring anemia until we saw the post-mortem findings.

For about a week or ten days before her death she passed some black, tarry stools, so that we felt fairly certain that she must have some ulcerating or tumorous process in her intestinal tract somewhere and in light of the findings it clarifies the cause for the recurring anemia.

I feel that this is rather an unusual case, both in the place of metastasis and the type of formation of the metastatic process. In retrospect, I am wondering if she did not have recurring attacks of intussusception, which relieved themselves, and that was causing her upper abdominal pain which was interpreted as being due to the gall bladder. It is very difficult oftentimes to differentiate between acute gall bladder and acute intestinal obstruction clinically and when both are present at the operating table it is important that neither be overlooked. The symptoms of small bowel tumors are those of anemia and of obstruction.

Diverticulum of the Gall Bladder

Review of Literature and Report of Case

By

MEYER GOLOB, MD
NEW YORK NEW YORK

ORDINARILY the writer would not feel obliged to apologize for reporting a single case study of an anomaly. A review of the clinical literature shows that between 1923 and 1943 twenty articles were published on diverticulosis of the gall bladder. Nine of these originated in the United States and eleven abroad (1). The paucity of reports on the diverticular anomaly, especially when we consider the advances made in cholecystography, attest to its rarity. But this particular case lacks operative evidence. The patient, after two years in which she has been conscious of discomfort in the upper abdomen, refuses to permit operation unless an emergency arises. Since the writer may never know where and when such an operation was performed and what the operative findings were, he feels that it is best to report the case as it stands. Although the roentgen findings on which this report is based would be greatly enriched by

surgical evidence, the X-ray data appear to be of sufficient interest in themselves. Should other writers, in encountering similar shadows, be more fortunate and have surgical confirmation, this report of pre-operative evidence of an anomaly will have served a purpose. Perhaps many similar cases were missed roentgenologically because of non-filling of the diverticula. On repeated cholecystography the case here presented showed only faint evidence of the anomaly. The interpretation of a diverticular shadow would have been missed without a reading in terms of the first cholecystogram, which unequivocally demonstrated an anomalous shadow.

CASE REPORT

Woman, multipara, aged forty-five. She had had three stormy pregnancies and several abortions. The pregnancies were attended with hyperemesis gravidarum, and required

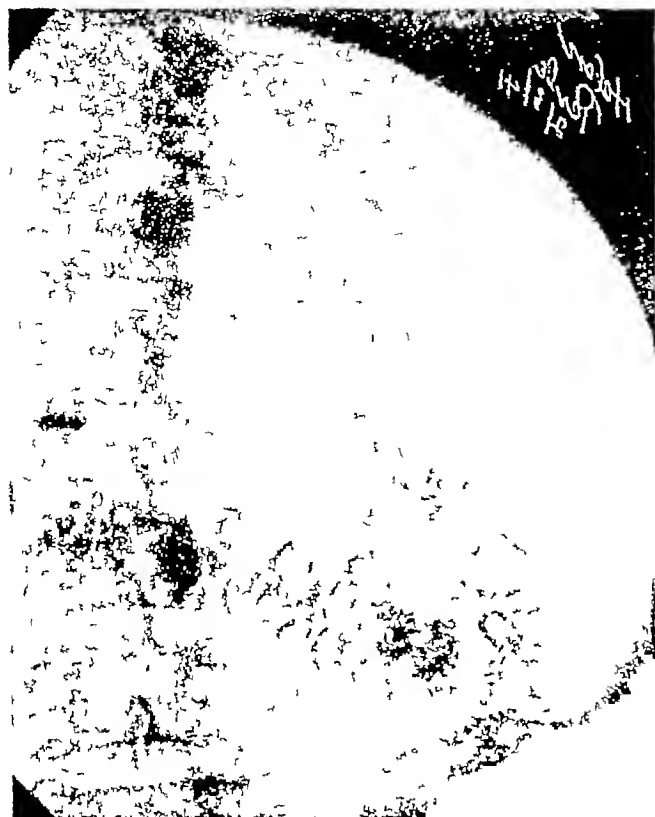


Fig 1

long periods of confinement to bed. The dominant symptoms were of several years' duration, and, descriptively, were non-referring in character. On inquiry she complained of belching, early evening distress and awareness of right subcostal arch, constipation with episodes of loose movements containing undigested food particles. There were no classic symptoms of cholecystic disease. In prone position she obtained ease in the right upper abdominal quadrant. For as long as she could recall, she had been unable to tolerate the weight of the corset in the right abdomen. No symptoms were elicited referable to the cardiovascular, renal, pulmonary or endocrine systems.

The physical findings were essentially negative, except for right subcostal arch tenderness, a sentinel pile and redundant perianal skin without a pruritic zone. Blood pressure readings were systolic 110, diastolic 80. Urine was negative for sugar and albumin, concentration normal. Gastric analysis yielded normal acid values, mucus 2 plus, occult blood intensely positive. Blood cytology was essentially negative. Blood sugar fasting, 66 mg, cholesterol 164, esters 57. The blood sedimentation rate was 26 mm in one hour.

Cholecystography, double dose technique, showed a normal sequence and no evidence of calculi, but an additional shadow appeared which was interpreted as a diverticulum of the gall bladder. After an interval of nine months cholecystography was repeated, with special attention to exact reduplication of the original technique. The viscus was less distinctly outlined, the anomalous shadow previously noted was but faintly discerned. Figures 1, 2, 3, 4 show filling, concentration and emptying of the viscus, 3 and 4 following the ingestion of a fat meal. Fig 4 demonstrates distention of the diverticulum from absorption of more of the opaque medium.

Roentgen study of the gastro-intestinal tract yielded, as its only positive findings, an appendix plastered to the inner aspect of the cecum and spastic colon constipation. Secondary evidence of pericholecystic adhesions was not detected.

Bringing the record to the present writing, after a

further interval of two years the patient still complains of belching, cannot stand the weight of clothes around her waist, "the right side is sick." Thus she expressed persistent awareness of her right upper abdomen.

DISCUSSION

It is not within the scope of this paper to discuss gall bladder anomalies as a class. It will confine itself to this particular anomaly, diverticulum of the gall bladder. Schaschnei, referred to by Rukstinat (2), placed in one group anomalies relating to the cavity of the gall bladder, including duplication of the viscus, bilobed gall bladder and diverticulum. I am of the opinion, however, that roentgenologically the pattern of publication is distinct and can easily be differentiated from that of a diverticulum.

Etiology. Diverticula are classed as congenital and acquired. Belief in the former rests upon results in animal tissues applied directly to human malformations. The latter is held to be the result of an inflammatory involvement of the gall bladder. Graham, Cole, Coppey and Moore (3) speak of "diverticular bladders—distinct vesicles or subordinate lobes, arising as buds from the neck of the embryonic gall bladder and usually associated with cyst-hepatic ducts (chiefly characteristic of ungulates)." Rolleston and McNee (4) suggest ulceration followed by weakening of the wall as causative of the diverticula, the implication being, therefore, that the anomaly is acquired rather than congenital. As possible etiologic factors Halpert (5) referred to hernia-like outpouchings of the gall bladder mucosa, of the size of a millet or hemp seed, described by Rokitsansky in 1842 as "small saccular dilatations of the biliary mucous membrane" which may appear to lie external to the cavity of the



Fig 2

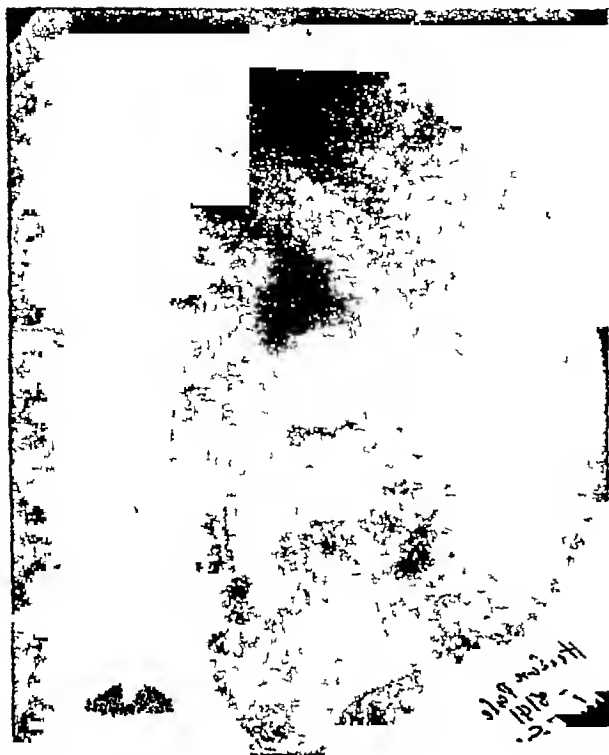


Fig 3

gall bladder. It is logically possible that such pouches might be sufficient to initiate a diverticulum. That a diverticulum might furnish an anatomic basis for its later development is borne out by microscopic findings in the case of Vastine (6). He writes, "There are many outpouchings of the mucosa between the muscle bundles of the middle coat (Rokitansky-Aschoff sinuses)."

Salient points of reported cases. In the case of Webening and Schondube (7) the diverticulum was large enough to interfere with the emptying of the stomach. Nadeau (1) dissected a diverticulum connected with the fundus of the gall bladder that perforated the surface of the liver. Rukstinat (2) reported three cases of congenital diverticulum of the gall bladder. Each diverticulum possessed the same degree of chronic inflammation as was noted in the gall bladder. In one of the diverticula and in one common bile duct, glands were found with potentialities for the formation of a cyst or adenoma. In one a carcinoma of the bile duct was found. In one case cholecystography warranted only a diagnosis of chronic cholecystitis, paracolic adhesions and slow emptying of the gall bladder. The operative findings revealed a pouch 2.7 cm in diameter, lined with cholecystic epithelium and speckled with lipid deposits. The second patient presented a clinical picture of thyrotoxicosis and died twenty-six hours after admission to the hospital. Autopsy revealed among other pathologic conditions cholelithiasis with an outpouching of the tip of the fundus. The diverticular lining was speckled with fat deposits in the same manner as the gall bladder. In the third case as in the first, the cholecystogram, after both ingestion and intravenous injection, revealed a pathologic gall bladder. The operative specimen showed a proximal and distal chamber the

first being the gall bladder with an aperture leading into a diverticulum which was larger than itself. Both linings were speckled with lipid deposits in the tips of the rugae. All three patients were women, and in the case of the two who were X-rayed no diagnosis of a diverticulum was made.

Gross (8) compiled data on one hundred forty-eight abnormalities of the gall bladder including nine diverticula. Toida (1) reported a diverticulum 8 cm in diameter in a girl five years old. The stalk of the sac was rich in Luschka's ducts, poor in blood vessels and devoid of inflammation, criteria of a congenital origin. That a diverticulum may be primarily involved and the gall bladder spared is attested to by the case of Abbott (9) who noted a diverticulum 15 cm deep at the neck of a gall bladder which was bound to the duodenum. Inflammation was present only in the diverticulum and had not affected the gall bladder. The advisability of operating on this anomaly, congenital or acquired, lies in its potentiality of involvement into complications by pressure on adjacent or neighboring organs. The case of Webening and Schondube (7) is one to point. A diverticulum the size of a man's fist, connected by a stalk to the fundus of the gall bladder produced pressure. The adherence between the gall bladder and the gastric antrum necessitated the resection of part of the stomach. The authors considered the diverticulum acquired. Pertl's case (10) is another instance of complication in which the diverticulum perforated the jejunum. In Nadeau's case (1) the diverticulum perforated the anterior surface of the liver. Several varieties of pseudo-diverticula are referred to by Rukstinat (2), eventrating pouches associated with cholecystitis being the most common, the wall of the sac containing muscle and connective tissue but no epithelium. Ross's case (11) is that of a pseudo-di-



Fig 4

vericulum a strawberry gall bladder, at the fundal end of which a marsupial-like pouch was discovered. It was considered acquired rather than congenital, and regarded as false, since the diverting pouch was associated with regional cholecystitis and the wall of the sac contained muscle and connective tissue but no epithelium.

That either the gall bladder or diverticulum may be normal and the other pathologic is evidenced by Nadeau's case, in which the former was markedly diseased. The diverticulum first appeared to the surgeon as an "adherent cyst" in the liver but proved to be a diverticulum communicating with the gall bladder. The entire gall bladder with the diverticulum was removed, leaving a "punched out" cylindrical opening in the liver. There was thus a pathologic gall bladder and normal diverticulum, considered congenital since no evidence of inflammation was found. The position of the anomaly could, however, be considered pathologic.

Summary. Pre-operative diagnosis of diverticulum of the gall bladder can only be made by cholecystography. Twenty papers have discussed the subject since 1923, some under the term of pseudodiverticulosis. Six cases were detected roentgenologically, not all were confirmed by operation. Some were diagnosed operatively and others at autopsy. That Rokstnat's three cases, reported in 1936, constitute about fifteen per cent of all recorded in the literature attests to the rarity of the anomaly. In contrast Vustine writes that it is not an uncommon finding at operation or autopsy, but that in spite of its relative frequency of occurrence pre-operative diagnosis is rarely made. Barsony (12) in 1927, and Barsony and von Friedrich (13), in 1928, reporting a case of diverticulum of the gall bladder cholecystographically detected and surgically confirmed, claimed that as far as they knew there were no previous reports of roentgenologic diagnosis and operative confirmation.

In the writer's case a diverticulum was diagnosed in an otherwise normal gall bladder. But the viscus and its anomaly may both be pathologically involved, or either one separately. Abbott's case was an instance where a markedly inflamed diverticulum arose from an otherwise normal gall bladder. It is interesting to note that in the present case the diverticulum shadow appears larger than that of the gall bladder (Fig. 3, 1). Contraction and expansion of the shadow and its

entire disappearance, roentgenologically, attest to the functional ability of the diverticulum as of the gall bladder tissue itself. And, in the case under discussion, it appears, roentgenologically, that both gall bladder and diverticulum were functioning normally, since they both filled and emptied.

From the literature we may deduce that a cholecystogram taken following a fat meal would show less decrease in size in the diverticulum due to absence of muscle fiber in its wall. It is therefore interesting to note that in the writer's case the shadow in Fig. 4, three hours after the fat meal, is much larger than that in Fig. 3, one hour after the meal. This increase in size may be considered evidence of continued absorption of the dye, and supports the belief in the diverticulum's inability to expel contents because of the absence of muscle fiber in its wall. The similarity of clinical pictures, including the case of the writer, is interesting, as is the fact that all patients were women. Sites were recorded at the fundus of the viscus, at its neck and intrahepatic. A diverticulum may cause environmental complications, as was demonstrated in the case of Pertl (10), "the tip of the gall bladder was adherent to the jejunum, and when freed a diverticulum of the gall bladder was found to have perforated the wall of the bowel." Deaver and Ashurst (14) reported a diverticulum large enough to press on the common bile duct and cause jaundice.

The case reported shows that a diverticulum may be visualized with a dense, homogeneous shadow on the first occasion, and present very faint visualization on check-up despite careful adherence to the original technique. On the basis of this, though no firm conclusion can be drawn from a single case, we may hazard that many diverticula of the gall bladder exist, but are not detected because of non-filling or poor filling with the opaque medium. A poorly visualized diverticulum harboring a stone, adjacent to a well filled gall bladder, might be interpreted as a positive shadow lying external to the lumen of the gall bladder. Pycnography would differentiate between renal stone and cholelithiasis. The constant relation of the diverticulum to the gall bladder shadow, however, the presence of a slight indentation in the outline of the gall bladder adjoining the shadow of the calculus or the diverticulum, the frequently laminated appearance or negative center of the calculus, these features would help to distinguish between renal and biliary calculi.

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Notes On Nutrition

Food Supplies in a Japanese Internment Camp Clinton N. Laird, Professor of Chemistry, Langan University, Canton, China, one of the internees in Hongkong, following its fall into the hands of the Japanese on December 25, 1941, writes regarding the kinds and amounts of food which were allowed the British, American and Dutch internees. Briefly it was estimated that 1000 calories a day per person were obtained in February and March, 1942, and about 2000 calories in April. Of 50 persons who had to consult the physician, each had lost an average of 34.6 pounds. Certain persons experienced a 20 per cent fall in blood pressure, and some ulcer patients seemed to improve on the high carbohydrate diets used. Beriberi existed in 30 per cent of the population of the camp. An unknown kind of intestinal complaint was common, also night blindness. Twenty-eight cases of scurvy responded to ascorbic acid treatment. One case of advanced pellagra and one case of acute sprue were seen. However, only 10 persons died, which was less than half the normal death rate of the colony.

Vitamin C and Wound Healing It was proved that ascorbic acid has much to do with the healing of wounds by personal experiments by Crandon, in which he subsisted on a low Vitamin C diet until the plasma ascorbic acid had fallen to zero, after which it was found that he was defective in healing experimental wounds, and this was corrected by the administration of the vitamin (J. A. M. A., 116:663, 1941). Animal studies have shown that operation wounds in animals on a high ascorbic acid intake are twice as strong after healing than similar wounds in animals fed a scorbutic diet (New Eng. J. Med., 226:469, 1942). Clinical study shows first that a low fasting plasma Vitamin C level does not necessarily indicate a low tissue reserve of Vitamin C. The tissue reserve may be judged by how many daily injections of 1 g. of ascorbic acid are required to bring the fasting level up to normal. Where nonradical operations were performed, more complications and deaths occurred in the patients with low reserves than in patients with high reserves. No correlation could be found between Vitamin C reserves and the morbidity in those subjected to radical operations (New Eng. J. Med., 227:247, 1942).

Thiamine Deficiency in Alcoholism Studies showed that patients suffering from "alcoholic" polyneuritis consume diets inadequate in various members of the Vitamin B complex and it was assumed by some that thiamine deficiency rather than the alcohol was the cause of the polyneuritis. The relationship between a high alcohol diet and the needed amount of thiamine is not clear. In the dog the use of pyruvate accelerates the oxidation of the alcohol, and the enzyme system at work contains thiamine as an essential component (J. Biol. Chem., 144:657, 1942). In the rat, however, it has been shown that ingestion of alcohol may decrease the thiamine requirement, delaying the onset of polyneuritis and death in animals fed a diet deficient in thiamine (J. Nutrition, 24:73, 1942). The only present possible conclusion is that the chronic alco-

holic requires thiamine for the combustion of alcohol but the requirement may be less than that necessary on the usual diet.

The Vitamin Content of Blood and Urine as Diagnostic Aids The use of blood and urine estimations of those vitamins which can so be detected has reached a stage of refinement, yet the information gained by single determinations may be of little value and certainly of less value than the method of "vitamin-tolerance tests." In these a known amount of the vitamin is administered and the quantity excreted in the urine subsequently determined. The theory is that if the tissues have been hungry for vitamins they will retain a large portion of the vitamin administered (New Eng. J. Med., 226:649, 1942).

Vitamin K and Hemorrhage During Birth Two sets of investigators have found that administration of Vitamin K to mothers before delivery decreased the incidence of hemorrhage at birth and significantly lowered infant mortality, while the third investigator noted no effect from this procedure (South Med. J., 35:289, 1942), (Am. J. Obst. Gyn., 41:765, 1941), (Am. J. Obst. Gyn., 44:433, 1942).

Carotemia Some people anxious to ensure sufficient Vitamin A have consumed 5 to 8 pounds of raw carrots per week for as long as 6 to 8 months and their skins became "carrots," which suggested jaundice. Persons with diabetes or nephritis tended to develop carotemia more easily than normal patients. If the blood serum is shaken with alcohol and petroleum ether, the lipochrome will be concentrated in the ether, whereas bilirubin is concentrated in the alcohol. No apparent harm came from the carotemia (Brit. Med. J., II:239, 1942).

Chronic Nutritional Deficiencies While the classical nutritional deficiency syndromes are those arising from rather severe degrees of undernutrition of relatively rapid onset, there has recently arisen a concept of nutritional deficiency which postulates that there may be ill-defined affections resulting from minor degrees of malnutrition acting over long periods of time, e.g., in man, over several years to a life time. In experiments on monkeys in which diets low in calcium, or Vitamin C, or both were used over many months of time, any symptoms attributable to the deficiencies were very slow in showing up. The author felt that there was no evidence that a chronic deficiency of both calcium and Vitamin C influenced the course of these animals other than what might be anticipated from an addition of their individual effects (Pub. Health Reports, 57:959, 1942).

Pernicious Anemia and Vitamin C It was found that one case of Addisonian anemia which had failed to give a reticulocyte response during nine days of administration of potent liver extract preparations, gave such a response within 5 days after being given, in addition to the liver heavy doses of ascorbic acid (300 mgs daily). This is a good point to remember in patients who are slow to respond to liver therapy (Lancet, II:278, 1942).

Thiamine Deficiency in Diabetic Rats Experiments with thiamine deficient diets in depancreatized rats, did not indicate that the presence of thiamine had any beneficial effect on the diabetes, and these experiments do not support the contention recently found in the medical literature that thiamine is of value in the treatment of human diabetes mellitus.

Removal of Fluorine from Skeletal Structures Fluorosis in animals and man is due to excessive intake of fluorine and the signs are exostoses in the adult ("poker back") and mottled tooth enamel in the young. It has been suggested the communal drinking water be treated with fluorine because teeth are made more resistant to caries by fluorine. However, experiments indicate that when excessive fluorine deposit has occurred in the bones of the body, it is difficult or impossible to get rid of it. Hence, the less fluorine anyone takes the better, since it may have only very slight or negligible bodily uses (Biochem J, 35 1235, 1941).

Nutritional Status of Great Britain From information available it may be concluded that the nutritional status of the British people is reasonably satisfactory except that there may be a deficiency of Vitamin C during winter months and the early spring. The hemoglobin level of the blood seems to be lower in women and children than before the war, and this may be attributable actually to a lowered protein and vitamin intake, rather than to iron lack (Lancet, I 395, 1942).

Ascorbic Acid Losses in Processing Grapefruit Juice Juice from flesh, first grade tree-ripened grapefruit averaged 41 mg per 100 g of juice. $3\frac{1}{2}$ minutes delay between extraction and pasteurization caused a loss of 6 per cent of ascorbic acid, while for 30 minutes' tank storage the oxidative loss was 34.7 per cent (Food Research, 7 382, 1942).

Tongue Changes in Nutritional Deficiency A good classification of "tongues" is suggested as follows—normal tongue, excessively coated tongue, grooved tongue (with a coat, with macroglossia, with wandering rash or with atrophy), pellagrous glossitis, riboflavin deficiency glossitis (magenta tongue), atrophic glossitis (with complete smoothing, slight general smoothing or marginal smoothing), geographic tongue (wandering rash), black (hairy) tongue (New Eng J Med, 227 221, 1942).

Deficiency States and the Biomicroscope Niacin deficiencies, as well as ascorbic acid deficiencies, can be detected by the biomicroscope, the former showing as tongue changes, the latter as gum disease. The marginal cases of deficiency are those in whom the biomicroscope should be of value, yet it is difficult for anyone to be certain just what changes as may be seen are actually due to the specific deficiency assumed to

be the cause. Moreover, using data and standards of his own, Kruse found that heroic and prolonged treatment with large doses of vitamin over many months had to be used in order to reverse the tongue and gingival processes regarded as due to niacin and ascorbic acid deficiency. Further work on this problem is needed (Milbank Memorial Fund Quart, 20 245-262-290, 1942).

Blanching Dried Foods In order to preserve the taste in dehydrated foods and to prevent instability after dehydration, it is necessary to inactivate or kill all enzymes present in the food being dehydrated. This is done best by blanching with steam. Easy chemical tests with hydrogen peroxide exist for determining the presence of active enzymes in dehydrated foods, and as government inspectors use these, so should the manufacturers (Food Industries, 14 51, 1942).

Evaporated Milk Versus "Filled Milk" Filled milks are evaporated skim milks to which have been added coconut fat or some other fat to replace the butterfat. The sale of filled milks is illegal in interstate commerce. Is there a hitherto unknown essential factor in butterfat not contained in other fats? One experiment indicated that evaporated milk and filled milk had approximately the same chemical contents as respects total solids, total fats, nitrogen and ash. Experiments to determine the growth advantages of butterfat over other fats are somewhat contradictory. There is a tremendous loss annually through the wastage of skim milk, equivalent to the protein content of 20 million beef steers, and the Dept of Agriculture now is working on the problem of making this available for human use (Nat Research Council, Reprint No 114, Aug, 1942).

Vitamin C in Children Vitamin C in breast milk can be determined by simple analysis, and normally the baby receives about 10 mg of ascorbic acid per day, increasing to 50 mg daily at the time of weaning. The lower content of Vitamin C in cow's milk justifies the inclusion of ascorbic acid in the infant's diet formula. Latent Vitamin C deficiency may be fairly common in children. A serum level of 0.7 mg of ascorbic acid to 100 ml serum indicates a satisfactory Vitamin C nutrition and a level below 0.3 g indicates a serious deficiency (J Pediatrics, 16 717, 1940). A supplement of 40 to 50 mg of ascorbic acid daily (about 3 ounces of orange juice) is sufficient to produce an optimal postabsorptive plasma ascorbic acid in children of the age of 5 to 13 years (J Nutrition, 23 195, 1942).

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Editorials

A DIETARY METHOD FOR THE REDUCTION OF GASTRIC ACIDITY

ELSEWHERE in this issue appears a contribution by Frederick Hoelzel of the Department of Physiology, University of Chicago, which should be very carefully read by all clinicians interested in the problems of gastric acidity. Hoelzel probably has con-

ducted over a period of many years the most unemitting series of nutritional and gastro-intestinal self-examinations ever recorded in medical literature. His paper of only a few pages represents many years of work. The chief points which this work indicate are obvious, viz, that a diet high in protein and fat, low in carbohydrate and rather low in calories, reduces

the fasting gastric secretion of acid, by reducing the hydration of the body. On such a diet, as the weight of the individual fell, so did the gastric acidity. With increased calories, taken as carbohydrate, the body weight rose, hydration increased and with it, the gastric acidity. Others, no doubt, will attempt to confirm his findings.

It may occur to some clinicians that here lies a possible method for the control of gastric acidity in the treatment of peptic ulcer. It ought to be a very simple matter to prescribe for the ulcer patient a high protein, high fat diet, low in carbohydrate and in total calories and to follow the patient's acid secretion curves during periods of weight loss, and to observe whether such a diet gives the pain-relief experienced by alkali administration and simple frequent feedings. If such treatment should be found to act as effectively in preventing pain during the periods of ulcer sensitivity as the Sippy type of treatment its simplicity should recommend it both to the patient and the doctor. Even if alkalis had to be used at the inception of treatment, they might soon be given up, as soon as sufficient de-hydration had been induced. There is perhaps no more promising clinical experiment just now in connection with ulcer therapy than the application of these principles which are so plainly set forth in Hoelzel's current contribution.

THE EFFECT OF BILE ON GASTRIC ACIDITY

YEARs ago it was suggested that the operation of cholecyst-gastrostomy might be a good one for the relief of ulcer. The theory was that bile in the stomach would inhibit gastric secretion.

At the last meeting of the American Physiological Society, Kaulbersz and Winfield from Wayne University reported that the introduction of bile into the fasting stomach of dogs provided with a Heidenhain pouch had no influence on the secretion of acid in the pouch as brought out by an injection of histamine. The same experiment in dogs with Pavlov pouches produced an increase in the secretion of acid. In dogs with a gastric fistula the giving of bile greatly increased the acidity of the juice obtained with histamine.

The authors conclude that bile when put into the stomach, increases gastric acidity but after it gets into the bowel it inhibits it. Certainly, the pouring of bile into the stomach would not seem to be a good treatment for ulcer. (Federation Proceedings I Part 2, p. 45, 1942)

WAR NEUROSES

IN Sir Arthur Hurst's recent book on the "Medical Diseases of War" is an interesting chapter on anxiety neuroses written by that able psychiatrist the late T. A. Ross. In it, he points out, first, the importance of a bad nervous inheritance in preparing the soldier for a neurosis and a lifetime of dependence on the Veteran's Bureau. Second the nervous child with a bad nervous inheritance usually has to be brought up by a neurotic mother and this makes matters worse. Usually she, with her constant fear of disease, gives the boy the idea that health is a very precarious thing.

As Ross says it is extremely unfortunate that draft boards are so concerned with standards of physical

fitness that they let psychopath after psychopath go on into the Army. Such men are usually weaklings and misfits who can never be good soldiers, and who will only turn into the type of disabled veteran who spends the rest of his life demanding that his congressman get him special medical treatment and a larger pension. Ross points out that the average soldier is a bit of a child who has to be taken care of by his officers. The French are constantly recognizing this fact as their officers address their men as "mes enfants."

Ross emphasizes the tremendous importance of not saying anything alarming to the soldier who has just been brought in injured. Naturally, his main thought is, "How badly crippled am I going to be?" and it will be so easy then for the surgeon to suggest, by some carelessly uttered word, that the situation is a hopeless one. If the soldier gets this idea he may go on for years with a crippling neurosis due to fear. Worse yet, like many neurotic persons he may fail to tell anyone of his fear. He may keep on as he is, either because he is ashamed to admit he is fearful or because he is afraid of hearing the worst. Many persons with a beginning nervous breakdown are terribly afraid that they are going insane but they will not mention this devastating fear to the attending physician. As Ross says it is impossible to treat effectively an anxiety state without finding out just what the patient is anxious about. Often even when the soldier is physically injured, his main trouble and the one which keeps him disabled is his fear of the future.

Ross felt that in the last big war shellshock would never have been heard of so frequently if the soldiers hadn't discovered that this diagnosis would get a man sent back from the front. One trouble with soldiers is that they are so afraid of being shamed by being called neurotic or being told that they have a neurosis. Hence, every effort should be made to get the soldier to see that it is not a disgraceful thing to be nervous.

Highly significant, is Ross's statement that during the last war the military authorities were much too reluctant to give in and admit that it was useless to return to the front line, men with a chronic neurosis. Such men only cracked up again. Ross doubted whether overwork is a common cause of neurosis. Worry is much more important.

The break-up of family life and the long separation of husband and wife caused by war duty has a serious effect on some men who become jealous and suspicious, and wonder what the wife is doing at home. This tends to wreck the nervous system and to interfere with the man's work. For this and other reasons, big efforts are now being made to supply soldiers with a constant stream of letters from home.

THE RESEMBLANCE OF GENES TO VIRUSES

IN an unusual article on the physiology of the gene, in the July, 1941 issue of *PHYSIOLOGICAL REVIEWS*, Sewall Wright has called attention to some resemblances between genes and viruses. The most essential property of a gene is, of course, its capacity to bring about the production of an exact duplicate of itself. There is an analogy to the growth of crystals through a peculiar type of molecular arrangement. There is a difference, however, in that in the gene, duplication must be associated also with repeated

fission and separation and reproduction of the two parts

Among crystals, the closest analogies to the gene are to be found in the nucleo-proteins that are associated with the viruses. They have somewhat the same property of auto-synthesis and reproduction. As is now well known, some of the viruses have been crystallized. Viruses resemble genes in that they can be inactivated by Roentgen-rays, and through radiation they can be given new specificities so that offspring of the treated one will be different from the parent.

It is remarkable to see that within a few years after

the discovery of genes, a man can write 41 pages and quote 274 authorities on the chemistry of these tiny bodies!

ERRATUM

In the case report of the article by Dr. Leonaid Cardon entitled "Generalized Pruritus Due to Carcinoma of the Stomach and Cured by Gastrectomy" which appeared in the February issue of this Journal, it was stated that "At the present writing (9-1-42) he weighs over 100 lbs." However, this date was incorrect, and should have been 12-30-42.

Abstracts of Current Literature

FRANKLIN HOLLANDER, Associate Editor in Charge of Abstracts, New York, N. Y.

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

DINSMORE, R. S. *Diverticulum of the Esophagus*. *Cleveland Clin. Quart.*, 9, 187 Oct., 1942.

Two cases of esophageal diverticulum occurring in brothers aged 61 years and 51 years are reported. It is not thought this condition is familial. Both of these cases had persisted for four or five years during which time the diverticula had shown evidence of enlargement and symptoms had increased in severity. Both cases were treated with complete success by one stage operations. The author is personally familiar, from his own experience, with single stage and two stage surgical procedures and believes each has its special advantages in selected cases. He prefers the one stage operation as technically easier and safer whenever it can be employed. His technique is carefully described. The report constitutes a very interesting and informative contribution, even to the physician not primarily interested in surgery.—Sam A. Overstreet.

HENRY T. C. *Ulcerio-Membranous Stomatitis*. *Brit. Med. J.*, 4261 273, Sept., 1942.

Among 90 cases of ulcerio-membranous stomatitis, 87 were found to be Vincent's disorder and 3 were atypical. Most of the cases of atypical ulcerio-membranous stomatitis which have been reported bear a superficial resemblance to Vincent's angina but differ from this in the degree of toxemia they cause, the presence of complications and the relatively high mortality. In some instances the cases

of ulcerio-membranous stomatitis seen represent the oral manifestations of such diseases as pemphigus, erythema multiforme, or dermatitis herpetiformis.

The author describes 3 cases of atypical ulcerative stomatitis in which marked prostration and toxemia occurred, associated with conjunctivitis. In two cases there were skin lesions. Streptococci were isolated from the mouth lesions of all the cases, being hemolytic in those with skin lesions and non-hemolytic in the other. None of these cases responded to sulfonamide therapy, although all recovered after transfusions.—Henry Tumen.

PENNES, A. E. *Leiomyosarcoma of the Esophagus*. *Am. J. Roent. Rad. Therapy*, 48 336, Sept., 1942.

Pennes reports a case of leiomyosarcoma of the esophagus, which produced a roentgen filling defect resembling carcinoma, except that there was an extrinsic mass in the mediastinum connected with the esophageal tumor. The extension of the tumor into the mediastinum is an outstanding feature of the case. Although intra- and extra-luminal tumors have been noted in the stomach, it is a rare occurrence to demonstrate them in the esophagus. Sarcoma of the esophagus is either an ulcerative or polypoid growth. The tumor is frequently largely extra-luminal.—Maurice Feldman.

GRACE, E. J. *Control of Massive Esophageal Hemorrhage Secondary to Liver Damage (Cirrhosis) by Ligation of the Coronary Vein and Injection of Sodium Morrhuate*. *Ann. Surg.*, 116 387, Sept., 1942.

The pathogenesis of esophageal varices is first discussed rather completely. Then the author goes on to discuss the evolution of the various techniques for the control of hemorrhage from bleeding esophageal varices: injection of sclerosing solutions, ligation of the coronary vein of the stomach, splenectomy, omentopexy, etc. He then discusses the case of a far advanced cirrhotic with ascites, with poor liver function, and multiple hemorrhages from bleeding varices. Following celiotomy the coronary vein and several other smaller veins close to the former were ligated and sclerosing solution (sodium morrhuate) was injected. The veins of Sappey on the undersurface of the diaphragm were also ligated. The spleen was bound down due to an old perisplenitis and was not removed. A month after the first operation omentopexy was performed. The patient was then given the benefit of modern knowledge in the way of therapy for liver damage and 2 years after the above surgical procedures the man felt fine, had good liver function, had no ascites and worked daily as an elevator operator. He had had no more gross hemorrhages.—Frank Neuwelt.

STOMACH

McCLURE, C. W. AND JANKFELS, I. R. *The Clinical Application of Gastroscopy*. *New Eng. J. Med.*, 227 548, Oct., 1942.

Roentgenology and gastroscopy are complementary methods, and are neither competitive nor antagonistic. Their combined use can reduce con-

siderably the error in gastric diagnosis. Gastroscopy may lead to better differential diagnosis of lesions found radiologically or may lead to detection of affections not found by X-ray.

The lesion most frequently encountered on gastroscopy is chronic gastritis (over 40 per cent of all cases examined). The authors, however, emphasize that in 50 per cent of these cases, the gastritis is secondary either to another intragastric or to an extragastric disease. Gastritis may simulate clinically either peptic ulcer or gastric neurosis.

Gastroscopy is the only clinical method to ascertain presence, type and distribution of gastritis. Only gross variations from the normal are of diagnostic significance for the gastroscopist, the margin of error is considerable in minor variations. In peptic ulcer of the stomach the use of the gastroscopy is recommended for detection when radiology has failed, for the elimination of malignancy, and for the follow up of the healing process. In gastric cancer not involving the orifices, gastroscopy may lead to an early diagnosis, and it may help detect tumors of the posterior wall or the cardia which often give inconclusive X-ray findings. For diagnosis and follow up of benign gastric neoplasm, gastroscopy is the most useful and exact method — Manfred Hess.

BOWEL

GLOVER D. M., SMITH S. AND EITZEN, O. *Multiple Atresia of the Small Intestine*. *Ann Surg*, 116 337, Sept., 1942.

Multiple atresia is one of the rarest causes of intestinal obstruction in the newborn. This case presented eight separate and complete points of occlusion of the small intestine. A two months premature infant vomited everything given her during the first two days of life. There had been no passage of meconium or stool. X-ray studies showed the stomach and duodenum to be tremendously dilated with gas but the rest of the intestine was collapsed. A small amount of barium visualized the distended stomach and first two portions of the duodenum. The third portion of the duodenum seemed to lie anterior to and below the stomach and came to a blind point of occlusion behind the stomach. At operation the duodenum was found to end blindly in the region of the duodenojejunal junction. The caecum and appendix were just to the left of the midline below and behind the duodenum. A small loop of bowel was anastomosed to the blind end of the duodenum by an end-to-side method. Post-operatively the infant lived two days, took food by mouth, passed one small stool, but then died. Autopsy revealed that in addition to the blind ending of the duodenum

seven other areas of atresia were found in the jejunum and the ileum. A loop of ileum 8 cm from the cecum had been utilized in the previous operation, the stoma was found to be small but patent and no more obstructions found distal to the anastomosis — Frank Neuwelt.

DUCKETT, J. W. *Symposium of Intestinal Atresia*. *Intestinal Obstruction in the Newborn*. *Ann Surg*, 116 321, Sept., 1942.

Surgical treatment of congenital intestinal obstruction in the newborn is now established on a successful basis. Much of the credit for this achievement must go to Ladd who has done most to develop this field of surgery in this country. Congenital obstruction of the intestine should be suspected whenever a newborn baby vomits persistently soon after birth. The vomiting quickly becomes projectile and everything taken by mouth is lost when the obstruction is complete or nearly so. When the obstruction is incomplete or intermittent, the diagnosis may become difficult to make. Anatomically the lesion may be intrinsic or extrinsic the former being more frequent. The intrinsic lesion results from failure of reestablishment of the bowel lumen during the early weeks of foetal life. Complete atresia or stenosis may result, the latter of course being more amenable to surgery. Extrinsic obstruction is usually due to incomplete rotation of the colon associated with abnormally placed bands or folds of peritoneum which impinge upon the lower half of the duodenum most frequently.

The author then presents six case histories and discusses them briefly. He emphasizes the necessity for thinking of the condition in case of newborn infants who vomit promptly after birth and have neither birth injuries nor infection. The author was impressed by the use of concentrated plasma for post-operative treatment in these cases. A technical detail is the use of very fine cotton thread (No. 100) as the only suture material — Frank Neuwelt.

COX, M. E. AND PARKER, E. F. *Myo-Epithelial Hamartoma of the Ileum with Intussusception*. *Ann Surg*, 116 355, Sept. 1942.

This is the case report of an unusual benign tumor-like formation of developmental origin composed of duct-forming epithelium and smooth muscle occurring in the wall of the ileum of an infant and associated with intussusception. Such tumors are considered to be heterotopias of developmental origin, derived from misplaced epithelial buds or diverticula during the process of development of the intestinal tract. Clarke has advocated that such localized tumors of the

gastro-intestinal tract composed of epithelial and smooth muscle structures, regardless of their relative proportions and degree of differentiation, be regarded as myo-epithelial hamartoma. In the present instance a nine month old negro infant had developed an intussusception, operation revealed an ileocolic type of intussusception with a small tumor 1 cm in diameter along the antimesenteric border of the ileum where the intussusception began. This mass was excised locally and the infant died several hours later. Sections of the tumor showed it to be composed of single and multiple groups of closely arranged duct-like and cystic spaces surrounded by irregularly arranged interlacing bands of smooth muscle. The epithelium lining the duct structures was of the tall columnar undifferentiated type with eosinophilic cytoplasm and prominent basal nuclei, not unlike that of pancreatic duct epithelium in its appearance — Frank Neuwelt.

LIVER AND GALL BLADDER

ALLEN, A. W. AND WALLACE, R. H. *Drainage of the Common Hepatic Duct*. *S. G. O.* 75 273, Sept., 1942.

The authors believe that when the common duct has been opened drainage through a suitable tube to the outside should be routinely established. This will materially help to avoid bile peritonitis which carries a high mortality rate. Whistle tip catheters are adequate for drainage of the common duct and the tube should point toward the liver if the duct is small. An open end tube will allow for easier escape of bile. It can be removed without injuring the suture line in the common duct, and there is a minimal amount of drainage after its removal. Utilizing a vertical paramedian incision, one may reduce the morbidity caused by wound infection, dehiscence, and hernia by providing a carefully placed lateral stab wound (in Morrison's pouch) through which the tubes may be brought out — Robert Turell.

SAINT J. H. *Acute Cholecystitis and Its Rational Treatment*. *S. G. O.*, 75 323, Sept. 1942.

The pathologic changes which occur in the gall bladder are produced by acute obstruction of its outlet and acute inflammation of its wall. Saint stresses the obstructive factor and designates the lesion as acute obstructive cholecystitis. As a result of the obstruction and inflammation, intravesical tension in the gall bladder occurs. The tension may be so acute as to interfere with the blood supply and eventually may cause gangrene of the gall bladder which is followed by rupture. In forty of the author's 44 cases, stones were present. Cholecystostomy was performed in 37

cases and cholecystectomy in 12. The preponderance of cholecystostomies was due to the fact that they represent the author's earlier operative experience. As a result of the follow-up studies of cholecystostomies, Saint now believes that after an attack of acute cholecystitis, the gall bladder will only resume reasonably good function in a minority of cases; therefore he advocates cholecystectomy whenever the patient's general condition permits and when this procedure can be carried out satisfactorily.—Robert Turell

ELKELES, G AND MIRIZZI, P L. A Study of the Bacteriology of the Common Bile Duct in Comparison with the Other Extrahepatic Segments of the Biliary Tract. *Ann Surg*, 116 360, Sept., 1942

The authors made a systematic study of the bacterial contents of the common duct in addition to similar observations of gall bladder contents, wall of the gall bladder and the duodenum. Choledochal bile was obtained through the wall of the duct only in those cases in which the duct was to be explored; in other cases an olive-tipped cannula was introduced into the common duct through the cut end of the cystic duct. They found the following: (1) Choledochal bile is sterile in about 60% of cases with disease of the extrahepatic bile ducts. (2) Common duct bile is sterile in about 75% of cases of uncomplicated chronic calculous cholecystitis and atrophic sclerosing cholecystitis. Results are similar in cases of empyema or hydrops of the gall bladder where the latter is the only organ affected. Choledochal bile was frequently infected where complications were present such as pericholecystitis, hepatitis, odditis, or a dyskinesia. (3) Stagnation of common duct bile due to dyskinesia or stenosing odditis without stone predisposes to infection of this duct bile. (4) Stones in the common duct were the most frequent cause for infection of choledochal bile, occurring in 89% of such cases. (5) Bacterial infection of the common duct is always associated with infection of other parts of the biliary system and the bacteria found are generally of the same species. (6) Choledochal bile appears to have strong bactericidal powers.—Frank Neuwelt.

PANCREAS

LAMPSON, R S. Acute Pancreatitis. *Ann. Surg*, 116 367, Sept., 1942

Another article calling attention to pancreatitis and emphasizing the value of conservatism in the treatment. The author reports 29 cases which were diagnosed clinically, at operation or autopsy. Studies of diastase in fresh urine specimens were

made in suspected cases. An interesting point which is made is that 16 out of these 29 patients had 2-3 plus albumin in the urine, a finding "which is generally not emphasized and which undoubtedly reflects the severity of the disease." The mortality in cases where immediate operation was done due to mistaken diagnosis pre-operatively, was 33%. In patients subjected to delayed operation or not operated upon at all, the mortality was only 5%. Cholecystectomy or cholecystostomy was done in most cases of surgical intervention, whether immediate or delayed.—Frank Neuwelt.

ANEMIAS

McKIBBIN, J M, SCHAEFER, A E, ELVEHJEM, C A AND HART, E B. Studies of Hemorrhagic Anemia in Dogs. *J Biol Chem*, 145 107, Sept., 1942

These authors have produced both nutritional and hemorrhagic anemia in dogs and rats and have been able to demonstrate variable degrees of recovery by the addition of inorganic iron and copper salts. The presence of cobalt in the ration resulted in the most consistent failure in blood regeneration. Liver extract produced a consistent remission in all cases. The liver extract, therefore, seemed to provide additional factors not adequately supplied before. The present work is an investigation into the nature of the substance or substances present in liver extract responsible for this recovery. Phlebotomy and blood regeneration studies were made on dogs maintained on a highly purified ration supplemented only with synthetic vitamins—a procedure which the authors have demonstrated provides for normal growth over a considerable period of time.

The experimentally produced anemia is characterized by a fairly high erythrocyte count, extremely small cells, low hematocrit, low hemoglobin and low plasma iron. The administration of liver extract results in striking increases in hemoglobin, hematocrit, erythrocyte count, and plasma iron but the mean erythrocyte volume and saturation index remain practically unchanged. Iron deficiency did not seem to be the primary cause of remission failure. The active factor in liver seemed to be present in the organic portion. It did not appear to be pyridoxine, choline or Vitamin C. Cysteine or small molecular weight peptides containing cysteine may be effective by forming a cobalt-cysteine complex and thus preventing cobalt from exerting its toxicological effects. Bile salts and uropterin were productive of some improvement. The effects on blood regeneration with various liver precipitates seem to indicate that more than one substance is involved. When the various sub-

stances productive only of mild responses, were given collectively, activity comparable to liver extract was obtained. This mixture contained the synthetic B-vitamins, hog bile, salts, cysteine, increased iron, iodine and haliver oil. While this mixture resulted in the production of a relatively normal mean erythrocyte volume, the plasma iron levels were not increased as is the case when liver extract is used. This may indicate the existence of still another factor.

Dogs raised on a synthetic ration of sucrose and casein supplemented with thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid and choline appear to grow and develop normally. This is in decided contrast to the results obtained when mineralized milk was the ration employed as described above. It would seem that the liver extract adds a substance or substances not present in the mineralized milk but contained in the sucrose-casein mixture supplemented as already mentioned. When the dogs on this latter diet were bled and were allowed a supplement of cobalt in the diet, they were able to regenerate blood without the addition of liver extract. Cobalt had no deleterious effect. The success obtained with the synthetic ration seems to indicate that of all the substances necessary for blood building, relatively few are required in the diet and that the majority must be synthesized either in the tissues or in the intestinal tract. When the diet does not provide the few fundamental nutrients in proper quantity, impairment in the synthesis of body-made substances may result in a new type of deficiency. Mineralized milk appears to be sufficient for maintenance but incapable of providing the right constituents in proper quantity to meet the crisis of phlebotomy or an already existing anemia. Liver extract provides these substances either directly or indirectly through body-synthesis. This is also true of the synthetic diet supplemented with six vitamins.—Ira Manville

ULCER

COLLINS, E N AND WARD, G J. Current Trends in the Treatment of Jejunal Ulcer. *Cleveland Clin Quart* 9 159, Oct., 1942

The authors review their experience with 29 jejunal ulcers, all post-operative, four had had gastric resection and 24 gastro-enterostomy. Diagnosis was well established by X-ray and/or gastroscopic studies. The value of spot films and pressure technique is emphasized, and to the gastroscope is given considerable credit where X-ray findings are inconclusive.

Symptoms differ from those of ordinary peptic ulcer chiefly in that (1) pain is usually above and to left of umbilicus and (2) tenderness is more

often localized on the left side than high in the epigastrium. Hunger pain is of the same character as peptic ulcer pain, but night pain is a more prominent symptom. Chief emphasis is placed upon medical instead of surgical therapy. 18 cases were treated medically, 4 surgically and 7 could not be followed. Hospitalization is deemed a very important feature of management. Frequent feedings and alkalinization by use of aluminum hydroxide gel with persistence of a carefully regulated regimen for long periods after subsidence of symptoms are important. Following progress by X-ray or gastroscope is also important. Surgery is reserved for complications such as perforations, obstructions, massive hemorrhage, gastrojejunocolic fistulas.

The conclusion is reached that in the uncomplicated post-operative jejunal ulcer, adequate medical treatment persistently carried out until healing is assured with careful control of the patient's regimen for an indefinite period afterward (for 3 to 5 years or longer), constitutes the safest plan of treatment.—Sam Overstreet

BERK J E, REHFUSS M E AND THOMAS J E. *Duodenal Bulb Acidity Under Fasting Conditions in Patients with Duodenal Ulcer*. Arch Surg 45 406, Sept, 1942

The first part of the duodenum is the area most susceptible to the ulcerating influence of the acid gastric juice. This study reports data obtained on the acidity of the duodenal bulb under fasting conditions in patients with an ulcer in comparison with the acidity of the duodenal bulb during digestion in the same patients. Fasting normal patients were used as controls. It is hoped that this investigation will afford better criteria for evaluation of the acid factor in duodenal ulcer. Twenty six subjects were used in the experiment.

Gastric pH was 1.62 on the average for the patients with ulcer, and much higher than that of the normal subjects, which was 3.51. The duodenal acidity for those who had ulcers was 3.96, for fasting normal persons it was 5.60. It is concluded that the fasting values of gastric acidity are higher in patients with ulcer than in normal persons. The duodenal acidity is not only higher in fasting patients with duodenal ulcer, but the duodenal neutralizing power is lowered for a longer time. This impairment of duodenal neutralizing power is due in part to gastric hypersecretion and partly to a defective neutralizing mechanism in the duodenum itself. The neutralizing ability of the contents of the duodenal cap in patients with ulcer under fasting conditions is as good or better than that during digestion of an Ewald meal. The

simultaneously determined gastric and duodenal bulb acidity show no parallelism of behavior. During fasting, free acid is more often present in the first part of the duodenum of patients with ulcer than in normal persons, free acid of the duodenal bulb in fasting patients with ulcer tends to remain present longer than in normal persons.—Francis Murphy

DOWDIE, E. *Multiple Primary Nonspecific Jejunal Ulcers with Chronic Duodenal Dilatation*. Ann Surg 116 348 Sept, 1942

Both nonspecific jejunal ulcer and chronic duodenal ileus are rare but important lesions. In this case report, chronic duodenal ileus was a complication of jejunal ulcer. A 59 year-old male had suffered from dyspeptic symptoms for 10 years and had passed "black stools" on numerous occasions. He had never sought medical advice. During the past six months he began to vomit very frequently after meals lost 40 pounds in weight had a feeling of fullness in the epigastrium relieved by vomiting and was moderately constipated. X-ray examination revealed a high-grade obstruction in the region of the ligament of Treitz with marked dilatation of the stomach and duodenum. Upon laparotomy, the jejunum one inch below the ligament of Treitz was found to be adherent to the root of the mesentery and the bowel was almost completely constricted. The ligament of Treitz was sectioned and a lateral duodenojejunostomy was performed around the obstruction. The patient died 8 days later of a bronchopneumonia and post-mortem showed two jejunal ulcers, one shallow and one one cm in diameter, and just distal to this one another ulcer which was completely annular and had thinned the jejunum at this site.—Frank Newell

HOLMAN C AND CHENOWETH A. *The Problem of the Treatment of Secondary Peptic Ulcer*. S G O 75 314 Sept 1942

The conditions under which secondary ulcers may develop are as follows: (1) patients with ulcer diathesis, where psychic stimuli in the upper gastrointestinal tract in the presence of other factors play an important role, (2) hypersecretion of gastric acidity, (3) poor primary operative technique, (4) irregular habits of living, (5) overindulgence in tobacco and alcohol. Treatment, except for complications such as perforation or gastrocolic fistula, may be medical or surgical. Hemorrhage frequently responds to conservative therapy. If bleeding persists, dismantling of the anastomosis and a gastric resection should be carried out. If the primary operation was a gastric resection, the bleeding marginal ulcer should be ex-

cised and a revision of the stomach performed or if this operation is not feasible a secondary resection of the stomach should be instituted.

Conservative therapy for uncomplicated marginal ulceration will heal a number of ulcers. In the authors' group of 51 patients, the results of conservative treatment were good in 11 (21 per cent), poor in 35 (69 per cent) and 5 patients (10 per cent) died. Of the 35 poor results, 23 patients were subsequently operated upon for persistent symptoms. Medical successful treatment should include a period of rest in bed, a restricted diet, abstinence from tobacco and alcohol, and readjustment of the mental attitude and adequate accommodation of the patient to his environment. Of the 11 patients treated medically with success, 9 were able to make satisfactory mental adjustments while 29 of the 35 patients who failed to respond also failed to readjust themselves satisfactorily. It appears that expert psychiatric instruction should be a major constituent of adequate conservative treatment. Of the operative treatments gastric resection is the procedure of choice. This operation eradicates the secondary lesion and also the conditions that favored the original ulcer.—Robert Turell

SURGERY

SANDERS, R L. *Surgical Lesions of the Colon*. Southern Surg 11 652 Sept, 1942

Surgical lesions of the colon consist primarily of benign tumors, amebic colitis with abscess, chronic ulcerative colitis, diverticulitis, and carcinoma. The author presents a concise review of the clinical features of each of these conditions together with the indications for surgery and the type of operative procedure to be employed. Surgery of the colon consists mainly of incision and drainage of localized abscesses secondary to perforation, palliative colostomies and partial or complete resection. Two technical details which have materially reduced complications in the author's resections of the colon are (1) delayed closure of the colostomy wound and (2) the local use of sulfonamide drugs. Delayed closure of the colostomy wound consists essentially of a modified drainage, in the author's experience over a period of ten years, primary healing almost invariably follows. Either sulfanilamide or sulfathiazol powder may be introduced into both the peritoneal cavity and the incision as well as into the posterior wound following abdomino-perineal resections. No untoward effects have been observed from the use of 15 gms or more. Patients tolerate the drug remarkably well and their post-oper-

ative course has been excellent — Joseph B Kirsner

PEARSE, H E *A Simplified Anastomosis for Resection of the Duodenum and Head of the Pancreas* S G O, 75 339, Sept, 1942

Pearse described a simplified method of one stage resection of the duodenum and head of the pancreas, which restores the continuity of the biliary and digestive tracts, with only 2 anastomoses, and which retains the advantage of an antiperistaltic intestino-biliary union — Robert Turell

MORTON, C B *Total Gastrectomy* S G O, 75 369, 1942

The author described the technic of total gastrectomy in detail as carried out by him in 4 cases. Morton believes that while total gastrectomy is performed more frequently now than it was 10 years ago, this operation is still not commonplace. The paper is well illustrated — Robert Turell

PROCTOLOGY

COHN, I *Prolapse of the Rectum* Am J Surg, 57 444, Sept, 1942

This is a preliminary report of one case in which the author introduces and describes in detail his operation for prolapse of the rectum. Of the three main theories of causation he apparently chose the one in which prolapse of the rectum is a hernia. Any procedures which attempt to cure this process should fulfill certain indications: (1) resection of the prolapsed bowel, (2) suspension and fixation of the bowel, and (3) repair and restoration of the pelvic floor. Examination of the patient five months after the operation disclosed no evidence of prolapse and he had almost complete sphincteric control. The technique here suggested is a composite operation but is by no means the final answer to this problem — Michael W Shutkin

PHYSIOLOGY

SECRETION

SCHIFFRIN, M J AND GRAY, J S *The Effect of Urogastone on Gastric Secretion in Enterectomized Dogs* Am J Physiol, 137 417, Sept, 1942

The intravenous administration of 10 mg of urogastone effectively inhibited the volume of gastric secretion and the output of free acid in 12 experiments on 6 enterectomized dogs and in 8 experiments on 8 dogs with vagotomized total gastric pouches. No evidence was obtained which would indicate that urogastone inhibits gastric secretion through the liberation of enterogastone — Arthur E Meyer

MOTILITY

VAN LIERE, E J AND NORTUP, D W *The Effect of Carninatives on*

the Emptying Time of the Normal Human Stomach J Pharm Exp Therap, 76 39, Sept, 1942

Fluid extract of ginger, USP, in 1 cc doses was given to six subjects in a suitable test meal. Only one of the six subjects showed a statistically significant decrease in the gastric emptying time as ascertained fluoroscopically. Tincture of capsicum, USP XI, was given to three subjects in doses of 0.5 cc and to six subjects in doses of 1 cc. One individual showed a statistically significant decrease in the gastric emptying time, the other subjects were relatively unaffected. Six subjects were given 0.3 cc of oil of peppermint, USP XI. None of the subjects showed either a significant increase or decrease in gastric emptying. It was concluded that representative carminatives, such as capsicum, ginger and oil of peppermint may influence gastric emptying in certain subjects, but probably the gastric emptying time of the large majority of individuals is not appreciably affected by the ingestion of these substances in moderate doses — Arthur E Meyer

HENDERSON, S G *The Gastro-Intestinal Tract in the Healthy Newborn Infant* Am J Roent Rad Therapy, 48 302, Sept, 1942

A study of the normal anatomy and physiology of the gastro-intestinal tract in the newborn infant is presented by the author. Henderson reviews the embryology and data relating to the physiology of the fetal digestive system. A routine roentgenologic study was made in 110 infants to obtain data regarding the normal physiology and anatomic condition of the gastro-intestinal tract. A description of the stomach is given in both the supine and erect positions, and then differences detailed. It is pointed out that the peristalsis of the newborn stomach is very intermittent, and that gastric motility is usually not commensurate with visible peristalsis. No peristaltic waves can be seen but yet considerable amounts of barium may be seen leaving the stomach. The emptying time in the newborn is longer than in older infants, children and adults. During the first week or ten days after birth it is usual to find barium retained in the stomach at the end of eight hours and frequently at the end of 24 hours. The stomach was completely empty at the end of eight hours in only 30 out of 110 infants, whereas 30 infants had some barium remaining in the stomach after 24 hours. Of interest is the point made that the stomach empties more rapidly when the infant is held in the erect position. In most instances the jejunum is well filled, with partially segmented loops, and with little evidence of mucosal folds. The ileum shows isolated filled seg-

ments. In the colon there is rarely a continuous filling as is often seen in adults. The motility of the colon is generally more rapid in the infant. Most of the barium is evacuated in 24 hours, in the majority of infants — Maurice Feldman

ABSORPTION

ROBERTS, E AND CHRISTMAN, A A *The Influence of Lactose and Its Hydrolysis Products on the Absorption of Calcium* J Biol Chem, 145 267, Sept, 1942

The experimental literature dealing with the absorption and retention of calcium is, according to the authors, inconclusive as to the actual mechanism by which ingested lactose is effective in promoting these activities. Accordingly, they undertook to determine the influence of lactose and its hydrolysis products, glucose and galactose, on calcium absorption by determining the residual calcium at a given interval following the administration of a definite quantity of calcium by stomach catheter. When the average absorption in mg of calcium per rat per hour for each group is plotted against the mg of calcium fed, it was found that most of the points fell rather close to a line representing the absorption of 1 mg of calcium per hour for each 5.8 mg of calcium fed. Feeding the calcium in solutions of lactose, glucose, or galactose, instead of in water, did not increase the amounts absorbed — Ira Manville

METABOLISM AND NUTRITION

ANTOPOL, W AND UNNA, K *The Effect of Riboflavin on the Liver Changes Produced in Rats by P-Dimethylaminoazobenzene* Cancer Res, 2 694, Oct, 1942

Several substances are known to retard or impede the carcinogenic activity on the liver of the dye p-dimethylaminoazobenzene. A combination of casein plus riboflavin showed in marked degree this anticarcinogenic activity. The authors studied the effect of riboflavin alone on the liver changes caused by the feeding of the dye. The rats were kept on a synthetic riboflavin-free diet and a supplement of nicotinic acid instead of the riboflavin. In the absence of riboflavin the dye produced considerable liver damage in all animals. Nicotinic acid failed to prevent this damage. Riboflavin protected the animals from hepatic damage for about 4 months, but this protective action was lost after the animals had been exposed to the action of the carcinogen for more than 5 months. The liver then showed the same changes as those observed in riboflavin deficient animals after a few weeks of dye feeding. These changes ranged from hepatocellular

degeneration to carcinoma—Manfred Hess

RINEHART, J F AND GRENFBERG, L D *The Detection of Subclinical Scurvy or Vitamin C Deficiency Ann Int Med*, 17 672, Oct., 1942

The authors undertake to answer the question, "Is there a low degree of Vitamin C deficiency which undermines health but is not manifest as scurvy?" They assert that there is a wide variation in the concentration of ascorbic acid in the blood and give 0.0 to 1.3 mg as the range. This latter figure represents saturation and also the renal threshold in health. They further assert that if the fasting plasma ascorbic acid be found near the saturation level, then Vitamin C deficiency is marred by the next assumption that finding a low plasma ascorbic acid value does not indicate, of necessity, that the patient has suffered a Vitamin C deficiency. The daily requirement for Vitamin C has not been definitely established, they admit, but believe 100 mg per day will maintain saturation. The method used for determination of the degree of tissue depletion is conditioned by the fasting plasma ascorbic acid and the rise following 15 mg per kilo given orally. Patients showing a plasma level below 0.1 mg per cent showed demonstrable improvement on administration of Vitamin C and are classed as subclinical scurvy. Those showing a range between 0.3 and 0.8 mg per cent are classified as free of Vitamin C deficiency. The authors close with the suggestion that reticulocyte response following Vitamin C administration may prove to be a helpful objective index of deficiency.—Virgil E Simpson

DEANE, H W *A Study of the Hepatic Cell Mitochondria in the Fatty Liver Produced by a High-Sugar Diet Anat Rec*, 84 171 Oct., 1942

A number of cytologists consider that the mitochondria are the cell inclusions actively associated with the laying down of fat in the liver cells. Other cytologists feel that the mitochondria play no role in the deposition of fat droplets in the liver cells. This technical report contains the author's findings, using the high sugar diet of Barrett, Best and Ridout to produce fatty livers in mice. At about 2½ months of age the mice were placed on the high sugar diet for varying lengths of time, after which they were killed by a blow on the head and bled. Several pieces of liver from the left central lobe were immediately fixed in 10% neutralized formalin in a 0.9% NaCl solution. A modified Regaud technique was followed in preparation of the slides to demonstrate the mitochondria. The

author finds that certain morphological changes do take place in the mitochondria, yet he found no direct relationship between the latter and the deposition of fat. Restoration of mice to a normal diet results in defatting of the liver within a week and the mitochondrial picture becomes approximately normal. The writer makes certain interesting statements as to the biochemical processes and these cytological changes in the mouse liver during the course of carbohydrate and fat metabolism.—Frank Neuwelt.

SCHMIDT, L J, HUGHES, H B, GREFF, M H AND COOPER, E *Studies on Bile Acid Metabolism. II The Action of Alcaligenes Faecalis on Cholic Acid J Biol Chem*, 145 229, Sept., 1942

In a previous study, the authors showed that in the caecum of the guinea pig, cholic acid was converted by *Alcaligenes faecalis* to a derivative or derivatives which gave a negative Gregory-Pascoe reaction. The present study has shown the following factors to be concerned in regulating the rate of conversion of *Alcaligenes* of cholic acid: the air or oxygen supply of the culture medium, the concentration of cholic acid in the medium and the number of organisms in the inoculum. Also, it showed that the *Alcaligenes* converts cholic acid to monoketo-, diketo-, and triketo-cholanic acids. The end-product of this reaction (3,7,12-triketo-cholanic acid) has been isolated from digests in pure form and high yield. The conversion is due to oxidation. High concentrations of cholic acid inhibit the growth of the organism. The reaction is relatively rapid when the concentration of cholic acid is 1136 mg per cent or less and is blocked completely when the concentration is 1865 mg per cent or more. The larger the number of *Alcaligenes* in the inoculum, the more rapid the disappearance of cholic acid from the medium.—Ira Manville

PHARMACOLOGY

BLOOMFIELD, A L AND LEW, W *Prevention by Succinyl Sulfathiazole of Ulcerative Cecitis in Rats Proc Soc Exp Biol Med*, 51 28 Oct 1942

Spontaneous ulcerative cecitis in rats is characterized by superficial ulceration of the cecal mucosa, inflammatory thickening of the cecal wall, pericecitis and regional adenitis. The disease has similarities to regional enteritis in man. The primary cause is unknown. Paratyphoid bacilli are found. Succinyl sulfathiazole was employed to treat this condition. One group of 12 rats received the drug with their food, another group of 8 litter mates served as control. In the treated group no cecitis was found, whereas the control group had an incidence of 38 per cent of

the disease, in other groups of rats of the same age (85), the incidence of cecitis was 48%.—H Necheles

MISCELLANEOUS

DEAMER, S C AND CAPP, C S *Clinical Aspects of Gastro-Intestinal Disease in Childhood. Radiol*, 34 273, Sept., 1942

The authors discuss in summation some gastro-intestinal conditions without going into details. In childhood comparatively few conditions are seen which are very severe in nature. Celiac disease has raised great interest lately. This symptom is due to cystic fibrotic changes of the pancreas but also may be due to other causes. Hirschsprung's disease is easily recognized by a barium enema. The treatment is still unsatisfactory. Lumbar sympathectomy is done, or drugs of the mecloyl, prostigmine and syntropan groups are given. Bowel resection is not favored any more. Intussusception should be recognized early so that a life-saving operation can be undertaken. Peptic ulcers are not as rare as thought in former years. In cases of painless gross hemorrhage from the rectum we have to think of a Meckel's diverticulum. Rheumatic disease may manifest itself in the abdomen and simulates appendicitis, just like mesenteric lymphadenitis. This condition and abdominal allergy have been studied especially during the last years. The authors think that "a food eaten daily may produce symptoms once every three weeks, or even once every six weeks"—Franz Lust.

CROWIE, D *Intramural Intestinal Hemorrhage Brit Med J*, 4268 430 Oct 1942

This is a case report of a 51 year old woman who was admitted to the hospital with a two day history of abdominal pain, diarrhea, right lower quadrant tenderness, and rigidity. A diagnosis of acute appendicitis, possibly a pelvic appendicitis, was made. At operation the peritoneum was found full of blood. This was traced to a subserous hematoma of the lateral wall of the cecum. No perforation of the bowel was found and the cecal wall around the tumor was found to be normal. The cecum was resected. Examination after resection showed the presence of whipworms and evidence of acute and chronic inflammation of the cecum with intramural hemorrhage.

Crowie states that there are no similar cases in the literature. As possible causes of the hemorrhage in this case he considers (1) trauma, of which there was no history, (2) torsion of the cecum which had become reduced prior to operation but which had probably produced venous congestion and temporary rupture.

A Clinical Roentgenological Review of the Literature for 1942, Pertaining to the Digestive Tract

By

MAURICE FELDMAN, M.D.
BALTIMORE, MARYLAND

DURING the year of 1942 there has been a noticeable decrease of gastro-intestinal subjects published in the literature. The purpose of this review is to briefly survey the available literature on the subject of digestive diseases emphasizing the clinical roentgenologic aspects. As far as possible, all of the outstanding publications were reviewed and the major advances are herewith recorded.

ESOPHAGUS

Congenital atresia of the esophagus is now recognized with greater frequency than formerly. Worthy of notice is the newer procedure with which the condition can be demonstrated. Fuhrman and his co-workers report two cases which were demonstrated roentgenologically by means of injection of air into the esophagus.

Functional conditions involving the esophagus have been repeatedly described by many observers. Of interest is the report by Penner and Diuckerman, who have shown that dysphagia in Parkinsonism is caused by a segmentally located spasm in the esophagus which may be demonstrated by means of the roentgen examination. They consider the phenomena a distinct entity which may be relieved by the administration of belladonna alkaloids. In Plummer-Vinson's syndrome there is also a dysphagia associated with a hypochromic microcytic anemia. Ordinarily there are no complications occurring in this condition, however Elkeles reported an instance associated with a peptic ulcer in which he was able to demonstrate an ulcer niche defect with spasm in the esophagus.

Extrinsic conditions involving the soft tissues surrounding the upper esophagus may be recognized by means of the roentgen examination. Deep infections of the neck are at times due to a primary esophageal lesion. Orton stresses the role of the roentgen examination in demonstrating air in the cervical spaces as an important sign of peri-esophageal abscess. He points out that in esophageal perforation, edema and emphysema occur early and the retrovisceral and cervical space and the mediastinum may be involved by the spreading infection.

There have been numerous references to the frequent finding of gastric and duodenal ulcer associated with lesions of the lower end of the esophagus and cardia of the stomach. Dick and Huist found an esophageal ulcer in 2 out of 14 cases of diaphragmatic hernia with short esophagus. Huber and Anderson report 3 cases of hiatus hernia and one case of para-esophageal hernia which showed an ulceration in the herniated portion of the stomach, in one case of hiatus hernia there was a duodenal ulcer, there were 2 cases of short esophagus with ulceration at the cardia and another with ulceration at the pylorus, in 2 cases of megaesophagus one showed an ulcer just below the

diaphragm, the other in the prepylorus, in the latter instance there were multiple diverticulae in the lower esophagus.

Syphilis of the esophagus must be exceedingly rare, at least it is not generally recognized. In 7,000 examinations Peterson found 2 cases of luetic strictures in the esophagus.

Tumors of the esophagus usually present a characteristic roentgen picture, although it is difficult to give a histologic impression because of the similarity of these tumors. Dickes and his co-workers report a case of multiple polyps of the esophagus in which the X-ray showed multiple translucent areas resembling varices. The presence of extrinsic masses associated with esophageal disease should be carefully explored by means of the roentgen examination. Ordinarily in an uncomplicated case of carcinoma the lesion arises from the surface of the interior, thus one rarely observes an extrinsic mass. However, it is not unusual for lesions involving the wall of the esophagus to produce a tumor which expands both intra- and extra-murally. Such tumors usually arise from the connective tissue or muscle. Pennes reports an instance of leiomyosarcoma of the esophagus which produced an intrinsic filling defect resembling a carcinoma, in addition to an extrinsic mass in the mediastinum which was connected with the intrinsic tumor. The extension of the tumor into the mediastinum was an outstanding feature in his case. Schatzki and Hawes report 6 cases of intramural tumors of the esophagus in which the tumor mass was sharply outlined in the relief view. They point out that it may not produce obstruction, there may be an expansion of the esophagus at the site of the tumor. These extra-mucosal tumors are often demonstrated as a large soft tissue mass outside of the barium column.

STOMACH

Congenital anomalies of the stomach are more frequently recognized at autopsy but may be demonstrated by means of the roentgen examination. A case of obstruction of the stomach as result of a double septum with cyst formation had been reported by Metz and his co-workers. The cyst was of gastric origin which was probably formed by two septa. Feiliao reported a case of enterocystoma of the stomach presenting a duplication of the stomach. This anomaly is usually seen in the ileum or cecum and is known as enterogenous cysts.

The demonstration of changes in the mucosal rugae of the stomach has been noted with increasing frequency since the advent of special procedures which aid in their recognition. The mucosa is ordinarily loosely attached to the underlying tissues and at times may become redundant. In cases of marked redundancy

the X-ray will reveal a filling defect in the stomach that may simulate a neoplasm. There were a number of cases of redundant gastric mucosa reported during the past year. Moersch and Weir report a case in which the X-ray revealed a polypoid type of defect in the body of the stomach produced by a redundancy of the gastric mucosa. Rubin likewise reported an instance of gastric mucosa prolapsing into the duodenum, with malignant change. In this case the duodenal bulb was dilated and appeared cottony. He pointed out that there is a gastric deformity in the case of prolapsing gastric mucosa and that the condition may be demonstrable only in the prone position.

Many reports of various forms of gastritis appeared in the current literature. Many of these are of statistical value, but some offer new information regarding this condition. Pollard and Cooper found that nearly 25 per cent of 800 patients whom they had gastroscopied revealed a hypertrophic gastritis. They emphasize that the condition may account for hemorrhage or occult blood in the stools. Benedict likewise noted hemorrhage caused by gastritis. In 213 cases in which gastroscopic examination was made, hemorrhage due to gastritis was noted in 42 instances. The radiological aspects of gastritis according to Berridge fall into five groups. Besides the enlargement of the rugae and pseudo-polypoid formations he recognizes a blurring or veiling of the mucosal relief due to hypersecretion, inability of the muscularis mucosae to reproduce the normal resting relief and also a fibrosis of the deeper layers of the stomach causing a contraction of the lesser curvature forming a purse-bag stomach.

In recent years particular attention has been directed to the gastro-intestinal tract in children. However, very few studies have been made of the normal gastro-intestinal tract in the newborn infant. Henderson recorded factual information in this age group which is highly important. Of particular interest in the newborn infant were the findings of a slower emptying time of the stomach and the segmented pattern of the intestine and colon. In 110 infants, Henderson found the stomach was completely empty in only 30 instances after 8 hours and in 30 infants he noted some barium retained in the stomach after 24 hours.

Peptic ulcer in infancy and childhood have been reported with increasing numbers during the past year. With greater attention given to the roentgenologic examination in infants, a larger number of cases of peptic ulcer will be observed in this age group. Guthrie reported 9 cases of peptic ulcer (8 duodenal, 1 gastric) under 13 years of age, the majority were infants, in 6,059 post-mortems. Kraemer and Townsend report a case of gastric ulcer in a child of 6 years.

In adults the appearance of the ulcer crater is frequently characteristic of the type of ulcer as well as denoting the presence of malignant change. A clean-cut smooth ulcer niche defect projecting from the gastric contour along the lesser curvature is characteristic of a benign uncomplicated ulceration. Ulcer craters which show undermining edges or slight perforations should be so interpreted. On the other hand when the ulcer crater is intraluminal and surrounded by an area of edema infiltration or neoplastic-like defect the likelihood of it being malignant should be borne in mind. The demonstration of the meniscus sign in the roentgenologic examination of the stomach

is one of the characteristic diagnostic signs of an ulcerating carcinoma. Kirklin pointed out that not all ulcerating carcinomas give rise to the meniscus-complex signs.

The site of an ulceration often gives one a clue as to the possibility of it being malignant. Those occurring in the pyloric portion of the stomach, especially in the prepylorus have been considered as possibly malignant because of the prevalence of malignant ulcerations in this segment of the stomach. On the other hand those ulcers which occur at the pyloric sphincter or at the base of the cap close to the sphincter are more frequently benign. Kirklin and MacCarty note that the incidence of malignant gastric ulcer near the pylorus has been assumed to be disproportionately higher than that of ulcers situated elsewhere in the stomach. In recent years this observation has become questionable. The perennial problem of carcinomatous gastric ulcer is a challenge to the roentgenologist, gastro-enterologist and surgeon. The difficulties encountered in the pre-operative diagnosis of an ulcerating gastric carcinoma has been frequently stressed. Eusterman emphasizes some of the known facts regarding this condition, points out that a gastric carcinoma may masquerade a benign ulcer and may react to treatment in a similar fashion. The importance of recognizing ulcers occurring in the cardia of the stomach is stressed by Feldman. These ulcers are often unusually large in size and tend to produce hemorrhage.

Benign tumors of the stomach are usually recognized roentgenologically, presenting a more or less characteristic picture. Small discrete tumors may be overlooked. Heeks and Gibb report a case of gastric polyposis diagnosed gastroscopically. Dudley and his co-workers present a statistical study of benign tumors giving the incidence of 32 cases in 4,413 autopsies. There has been little reference regarding the appearance of the gastric mucosa in benign tumors. Schindler studied the gastric mucosa in cases of benign adenomas and found that adenomatous polyps are more prone to develop on the soil of an atrophic gastritis than in a normal gastric mucosa. He presents important statistical data regarding this phase of the subject. Thus in 2,167 cases there were 36 adenomatous polyps. In 310 cases of atrophic gastritis there were 15 benign adenomatous polyps. In the 310 patients with atrophic gastritis there were 43 suffering with pernicious anemia and in 6 of these adenomatous polyps were found.

Hemangioma of the stomach is comparatively rare, usually present a roentgen picture characteristic of a benign tumor. Gladden reported a case of cavernous hemangioma in the muscular layer of the stomach. Of unusual interest is the case of a carcinoid tumor of the stomach reported by Lemmer. This variety of neoplasm cannot be diagnosed by means of the X-ray, although if large in size may present signs of a benign neoplasm. Martel reported a case of ulcerated leiomyoma of the stomach.

The diagnosis of tuberculosis of the stomach had been a rarity but in recent years considerable impetus has been given to this subject since the advent of gastroscopy. Flexner and Baum report on the gastroscopic observations in pulmonary tuberculosis on 26 patients, found some form of gastritis in 21 cases. Of the 26 cases there were no evidences of ulcer, tumor or

tuberculous lesions. Browne and his co-workers studied the gastric mucosal changes in tuberculosis, noted an incidence of 0.22 per cent of gastric tuberculosis in 1,321 necropsies.

Syphilis of the stomach occurs in three forms the ulcerating variety being the more common. Rarely one may see the ulcer on the greater curvature. Of unusual interest is the case reported by Abegg, of a syphilitic ulcer on the greater curvature of the stomach.

The stoma in gastro-enterostomy has been given some consideration in this year's literature. The criteria of determining the pathologic or functional non-functioning stoma has not been clearly established, but the studies by Eusterman and his co-workers throw some light upon this problem. In 62 cases of non-functioning stoma the following etiologic factors were found, marginal or jejunal ulcer in 29, obliterating gastrojejunitis in 19, mechanical causes in 8 and physiologic dysfunction in 6 cases.

The complications of gastro-enterostomy are a rather frequent occurrence. According to Stein gastro-jejuno-colic fistula occurred in approximately 10 to 15 per cent of cases of gastrojejunal ulcer and in about 0.5 per cent of cases in which gastro-enterostomy had been performed.

The appearance of the mucosa of the stomach in gastric carcinoma presented a controversial problem which has been clarified by Schindler and Smith. In their study of 48 cases of gastric carcinoma, the gastric mucosa was normal in 10, a superficial gastritis was found in 8, atrophic gastritis in 25, and a hypertrophic gastritis in 5 cases.

Reports on sarcoma of the stomach appear to be increasing in frequency in recent years. Numerous statistical studies and case reports have been recorded. O'Donoghue and Jacobs found 6 cases of sarcoma of the stomach in 11,882 autopsies. They point out that the most frequent site of the lesion is in the antrum of the stomach. Walters found 110 cases of sarcoma of the stomach in 6,352 malignant tumors. Lemon and Broders report 14 cases, 11 were leiomyosarcoma, 2 hemangioendothelioma and 1 fibrosarcoma.

The stomach seems to be the most frequent organ involved in lymphoblastomatous tumors of the gastro-intestinal tract. Weber and Kinklin report 34 cases of primary lymphoblastoma of the gastro-intestinal tract, of which 25 were located in the stomach, 3 in the small intestine and 6 in the colon. They point out that there are no roentgenologic distinguishing features that would differentiate them from other neoplastic lesions. However, it has been stated that widening of the lumen and large hypertrophic rugae are frequently associated with this condition. Warren and Lulenski found 28 cases of lymphoid tumors among 3,152 malignant tumors of the gastro-intestinal tract, 10 were Hodgkin's disease, 10 lymphosarcomas and 5 were malignant lymphomas. Of the 28 cases, 14 were situated in the stomach, 6 in the small intestine and 8 in the colon.

Gastric bezoars are uncommon and only a small number of cases are reported each year. The roentgenologic appearance of gastric bezoar is more or less characteristic. The two following reports are of interest. Chont reported 9 cases of phytobezoar of the stomach, 7 of which were complicated with gastric ulceration. He has shown that hydrochloric acid is essential in the formation of peptic bezoars. Levy and Smith report a case of trichobezoar in which

the bezoar extended as a continuous mass from the stomach through the duodenum into the jejunum. This is very unusual, as ordinarily when seen in different segments of the gastro-intestinal tract, they occur as multiple separate masses.

Volvulus of the stomach is uncommonly seen, but may be recognized by means of the roentgen examination. Zimmerman reported a case in which the X-ray revealed the mucosal rugae could not be traced and the pylorus was behind and above a sacculi atypical stomach.

Frequent mention of the effect of vitamin deficiency on the function of the stomach is recorded in the literature. Of interest is the report by Diaz-Rubio and Roldan on the roentgen behavior of the stomach in pellagra, who studied 225 patients with pellagra, found many noteworthy features, namely, diminution of gastric peristalsis, gastric dilatation, retarded evacuation, atrophic mucosa and an intense aerogastria. In 22.3 per cent of the cases the stomach appeared to be normal.

DUODENUM

Congenital abnormalities of the duodenum are uncommon. A small number of cases are recorded each year. In atresia the roentgen examination will reveal obstructive signs. Impink and Glanville report a case of duodenal atresia. Wing and Clagett report a case of atresia of the duodenum presenting a diaphragm type in which a small opening was present, the X-ray showed a dilated stomach, with some barium passed through the colon in 24 hours.

The duodenal bulb is ordinarily not visible without the use of contrast media. However, the shadow may be visible when fluid passes through it. Feldman demonstrated the duodenal bulb shadow and pointed out that it has no clinical significance. Duodenal obstruction may be due to a number of conditions, either intrinsic or extrinsic in origin. The role in which abnormalities of the abdominal aorta play in the causation of duodenal obstruction has been given little consideration. An unusual case is reported by Partipilo and Wiltakis in which an abdominal aortic aneurysm produced pressure and displacement of the duodenum with obstructive signs.

Duodenal diverticula are commonly seen in the routine gastro-intestinal roentgen examination. They ordinarily produce no symptoms and complications are rather uncommon. The incidence of duodenal diverticula is given by Heishey who found 16 cases in 3,202 consecutive roentgen examinations. Usually the diverticulum is rarely over the size of a dime, but at times may become quite large in size producing pressure upon the duodenum and adjacent organs. The presence of gall stones in a diverticulum has been infrequently recorded. Rankin reported a case of a large sized gall stone in a duodenal diverticulum.

Duodenal ulcerations in childhood are infrequently recorded, however, in recent years a number of reports have been published. Franklin reported 2 cases of duodenal ulcer in children. Four cases of duodenal ulcer were reported by Clyne and Rabinowitch which clinically simulated acute appendicitis.

Various reports on duodenal conditions have been noted in past year's literature, most of which are of statistical value. Noteworthy is the report by Levine and Gordon of a case of complete biliary obstruction

complicating a duodenal ulcer in which the biliary obstruction disappeared following perforation of the ulcer. Psychosomatic changes in duodenal ulceration are presented by Morrison and Feldman, who noted a distinctive pattern in constitutional behavior associated with spastic, irritable states of the gastro-intestinal tract. An unusual case of duodeno-colic fistula caused by carcinoma is reported by Feldman, in which the fistulous tract originated in the colon and passed into the duodenum through a duodenal diverticulum. Cordiner discusses the roentgen changes in duodenitis, points out that the condition is commonly seen in the bulb, but may extend into the descending duodenum to the papilla. He presents the following signs as diagnostic changes in mucosal pattern, veiling of mucosal surface, broadening and thickening of mucosal folds, rigidity of folds and snake contour of the folds. A case of carcinoma of the duodenal bulb was reported by Hartzell in which the X-ray revealed a deformity produced by the tumor. Berger and Koppelman report a case of carcinoma in the third portion of the duodenum. Bisgard and Cochran report a case of sarcoma of the duodenum involving the first and second portions which extended into the head of the pancreas. Shakelford and co-workers report a case of myosarcoma of the ampullary portion of the duodenum which produced a large filling defect in the duodenum of an expansile type.

INTESTINE

A number of case reports of congenital anomalies of the intestine were recorded during the past year. Of particular interest was a case of intestinal obstruction reported by Duckett which revealed multiple anomalies, there was a stenosis of the duodenum, partial atresia of the jejunum and atresia and aplasia of the ileum. A case of multiple atresia of the intestine was reported by Glover and his co-workers, in which there were eight separate and complete points of occlusion associated with a non-rotation of the intestine. The X-ray in this case revealed a dilatation of the stomach and duodenum with an absence of air in the intestines. A case of intestinal stenosis in an infant was reported by Hancock, presenting an obstruction at the duodenojejunal juncture.

Meckel's diverticulum usually appear in the literature as single case reports, and in most instances following complications. They are rarely recognized by means of the X-ray, however, the diverticulum may be demonstrated at times. Ledoux reported a case in which the Meckel's diverticulum was seen in the four hour roentgenogram, there was bleeding from an ulcer on the margin of the diverticulum. Wilson reported 12 cases of Meckel's diverticulum. He quotes Schaetz as finding gastric mucosa in the diverticulum in 5 out of 30 cases. Waugh and his co-workers report 2 cases of Meckel's diverticulum associated with peptic ulcer, which had produced intestinal obstruction.

The physiology of the intestines has been a subject of frequent publication most of which pertained to the effects of vitamin deficiency and various pharmaceuticals on bowel function. Of importance is Puestow's contribution on intestinal motility, in which he noted a contrary motility between the small and large intestine when the small bowel is vigorously contracting, the colon was inactive, but when the colon contracts the small intestine appeared to be inhibited.

Primary non-specific ulceration of the intestine is

not generally recognized and cannot be demonstrated except in rare instances. The roentgen examination may show some form of complication as a result of the lesion. Dowdle reported a case of multiple primary non-specific jejunal ulcers in which the X-ray revealed a dilatation of the duodenum as result of an obstruction at the duodenojejunal juncture. Inflammatory disease of the intestine can be demonstrated by means of the X-ray, although early involvement may be overlooked. Phlegmonous enteritis is difficult to diagnose as such but the X-ray will usually show definite pathologic signs of disease. A case of acute phlegmonous enteritis involving the jejunum was reported by James, which showed enlargement and edema of the mucosal folds of the affected segment. A case of lipophagic granulomatosis of the intestine was reported by Sailer and McGann, in which the X-ray revealed signs simulating steatorrhea, i.e. gastric retention, dilatation of the duodenum, hypomotility of the jejunum, puddling of barium, irregular areas of spasm, segmentation of loops of intestine, etc. Susman and Wachtel reported 23 cases of granulomatous jejuno-ileitis described the stages of this disease, in the acute stage the picture simulates avitaminosis or sprue, while in the chronic stage there are characteristic signs of the infection, such as irregularity of contour, rigidity of the wall, fragmentation, multiple strictures, skip areas, etc. Brown and Donald reported 178 cases of regional ileitis, point out that although the X-ray is the most important single examination, it is not infallible. The locations of the lesion were jejunum 5 cases, jejunum and ileum 8 cases, lower ileum 99 cases, ileum and colon 66 cases. Only 46 of the 178 cases presented evidence of a fistula.

In volvulus of the intestine negative X-ray findings are generally noted, however, it should be emphasized that the diagnosis depends essentially upon the clinical manifestations. A case of volvulus of the ileum was reported by Kiernan, in which the X-ray was negative but at operation the mesentery of the ileum was twisted and gangrenous loops of ileum were found.

Tumors of the small intestine are not often recognized by the X-ray. This is especially true of the small non-obstructing variety. Carcinoid tumors of the intestine are rarely recognized because they are usually small in size and do not as a rule produce obstruction. However, carcinoid tumors of the intestine may produce intestinal obstruction. In 3,200 autopsies Dangremond found 8 cases of argentaffine tumors of the ileum, reported 2 cases of ileal obstruction. Miller and Herrmann in their report of 3 cases of carcinoid tumors of the small bowel, (2 in jejunum and 1 in the ileum) point out that the X-ray presents a kinking and buckling of the bowel at the site of the lesion, which they believe is suggestive of argentaffine tumors. The incidence of carcinoid tumors is given by Satoru, who found 72 cases in 26,384 surgically removed appendices. He found 2 cases of carcinoid tumors in the stomach, one in the gall bladder, one in the duodenum and 8 in the small intestine.

The roentgenologic manifestation of tumors of the small intestine is presented in a report of 41 cases by Weber and Kirklin. Chalkley and Bruce reported a case of neurofibromatosis involving the colon, small intestine and mesentery in which the X-ray showed a narrowing of the lumen of the terminal ileum, irregular contour, irregular cecal tip, the picture resembling

regional ileitis. Hemangioma of the intestine is rarely demonstrated. Christopher reported a case of hemangioma of the ileum, with negative X-ray findings. The importance of recognizing cases of mesenteric vascular occlusion clinically is stressed by Feldman, who points out that the X-ray generally yields negative results. Three illustrative cases were presented, in each the X-ray findings were not diagnostic.

Malignant tumors of the intestine are very difficult to demonstrate by the usual methods, but now may be recognized by instilling small amounts of opaque media directly to the affected part through a Miller-Abbott tube. A case of adenocarcinoma of the ileum with intestinal obstruction is reported by Flynn. A case of lymphosarcoma of the ileum is reported by Cope and Grant. Frank and his co-workers report 4 cases

APPENDIX

The roentgenologic diagnosis of appendiceal disease is inaccurate and unreliable. Roentgenologic findings should be interpreted with the greatest caution. Numerous publications on appendicitis are recorded each year, mostly from the surgical point of view. Mucocoele of the appendix may in very rare instances be demonstrated by means of the X-ray, but the complication of rupture of a mucocoele cannot be recognized. Chaffee and LeGrand report a case of a ruptured mucocoele of the appendix producing a pseudomyoma peritonaei. Jackman reported 2 cases of appendiceal fecalith, one of which was calcified, the other was revealed as a negative shadow in a barium filled appendiceal abscess. Tumors of the appendix are impossible to demonstrate because they generally produce a non-filling appendix. A case of myxoma of the appendix was reported by Laird and Nolan. Sanes and Patekin report a case of polyposis of the appendix associated with a polyp in the jejunum. In this case there was a non-filled appendix, with a mass about the size of a lemon.

COLON

Amebic dysentery presents a roentgenologic picture resembling other inflammatory diseases and an exact diagnosis cannot be made solely from the X-ray. Pendegrass and Chamberlain point out that the earliest roentgen evidence may be irritability and spasm of the cecum and that the ileum is not involved. Ochsner and DeBakey in their contribution on surgical amebiasis emphasize that amebic granuloma occurs more frequently in the cecum and sigmoid. Beine in his report of 74 cases of amebic abscess of the liver noted an hepatomegaly as a constant feature demonstrated by the X-ray, elevation and immobility of the diaphragm were early signs, pneumonitis and pleuritis occur secondarily as the condition progresses. Schulze and Ruffin have noted ulcerations in 52 out of 61 uncomplicated cases of amebic dysentery on proctoscopic examination.

Numerous contributions on diverticulosis of the colon have been published during the past year, most of which have some statistical value. Diverticulosis of the colon is readily recognized by means of the X-ray, but occasionally small discrete diverticula may be overlooked. On the other hand those that occur in the cecum offer many difficulties in diagnosis and are not often recognized until complications occur. Busch and Friedfeld report an instance of solitary diverticulitis of the cecum. Smithwick reporting on the inci-

dence of complications in diverticulitis found that 40 per cent of patients that come to operation are complicated, in 11.9 per cent abscess occurred, bladder fistula occurred in 13.1 per cent, and acute perforation occurred in 13.4 per cent.

There were a number of reports on benign tumors of the colon recorded in this year's literature. Of particular interest is the report on familial polyposis of the colon by Falk, who studied a family of seven, 6 of whom showed multiple polyposis of the colon. Mannheim and Peskin report an unusual case of spontaneous elimination of a lipoma from the sigmoid, the X-ray revealing a large filling defect in the sigmoid resembling a malignancy with an intussusception. Saint reported a case of lipoma of the ascending colon, producing an intussusception, in which the X-ray showed signs of a tumor and intussusception. Good reported a case of leiomyoma of the colon, in which the X-ray revealed a large expansile tumor mass in the transverse colon, producing a smooth filling defect with a semicircular deformity.

Reports on volvulus of the colon have been increasing in the past few years. The cecum and the sigmoid colon are the most frequent sites. Biowne and McHardy report 6 cases of cecal volvulus found in 172,158 admissions. Wolfer and his co-workers report a case which was demonstrated by means of the X-ray. Recurring or intermittent forms of volvulus are occasionally recognized. Ingelfinger reported a case of an intermittent volvulus of a mobile cecum in which the cecum was seen to rotate when the barium was injected into it through a Miller-Abbott tube. It was not seen in the routine gastro-intestinal and colon enema examinations. Hinton and Steiner report a case of recurrent volvulus of the sigmoid colon. River and Reed report 4 cases of volvulus of the cecum, point out that the plain roentgenogram will show signs of obstruction with distention of the ileum.

In recent years considerable impetus has been given to the diagnosis of lymphogranuloma venereum, and numerous cases are now being reported. The condition is generally seen in the rectum and usually leads to a stricture as a late manifestation of the disease. Bacon and Griffin describe the pathologic findings, noted that at first there is an erosion of the mucous membrane, followed by ulcerations, strictures, with dilatation of the bowel above the stricture and fistulous formations. Helper and Szilaygi reported 117 cases of rectal strictures due to venereal lymphogranuloma, point out that the disease always begins in the rectal pouch which reduces the size of the ampulla. They emphasize that the estimation of the total extent of the involved segment of the colon is not very accurate. Palmer and his co-workers report 10 cases of lymphogranuloma venereum, noted that it is a common cause of proctitis and sigmoiditis with and without strictures.

Fecalith of the rectum is not commonly recorded in the literature, although it is probably seen more often by the proctologist than the roentgenologist. Feldman reported a case of fecalith of the rectum, about the size of a small orange which produced a smooth filling defect in the rectal ampulla simulating a neoplasm, the clinical signs were those of a malignancy.

GALL BLADDER

Congenital anomalies of the gall bladder occur infrequently, although in large surgical clinics the con-

dition is seen with greater frequency. The recent literature contains numerous collected studies and single case reports. The roentgenologic recognition of these anomalies is rarely demonstrable, with the exception of the double gall bladder which may be portrayed. Finney and Owen reported 2 cases of absence of the gall bladder, collected 46 similar cases. Golob and Kantor report 2 cases of double gall bladders demonstrated by means of cholecystography. They directed attention that one of the gall bladders may be normal and one diseased.

The relation of the density of the cholecystographic shadow of the gall bladder to the iodine content was studied by Joffe and Wachoski, who found that 8.871 mg. of iodine per gram of bile produced a dense shadow while 2.5 mg. of iodine per gram of bile gave a faint shadow. Feldman studied 29 cases by comparative method, showed that by intensified cholecystography there was a definite improvement in the gall bladder shadow in cases of poor filling of the gall bladder. He recommends this procedure in all cases of poor filling, faint gall bladder shadows and non-filling of the gall bladder. Blumberg and Zisserman report on the necropsy incidence of cholelithiasis, found 89 cases of gall stones among 746 autopsies. A case of cholelithiasis in a newborn infant was reported by Spence. A peculiar appearance of gall stones has been commented on by Ortmyer and Connelly who report star-shaped radiolucencies in gall stones. They present a case with four large gall stones with fissuring or star-shaped or stellate fissures. This is believed to be due to a shrinking process. The authors point out that this phenomenon occurs in cholesterol-calcium-pigment stones and rarely in the pure calcium-pigment stones.

Calcification of the wall of the gall bladder is comparatively rare. It is easily recognized by means of the X-ray, presenting a characteristic peripheral calcification. It must be differentiated from small stones imbedded in the mucosa of the gall bladder. Gall stones are a frequent accompaniment of this condition. Hubert and his co-workers report 3 cases of calcification of the gall bladder. Calcium bile is occasionally observed, may be demonstrated in the preliminary scout roentgenogram. It is commonly associated with a stone in the cystic duct. McCall and Tuggle report 15 proven cases which were demonstrated roentgenographically.

Giardia lamblia infection of the gall bladder is infrequently reported in the literature. There is some controversy as to whether giardia infections interfere with normal visualization of the gall bladder. The experiences of different authors vary. In my own experience, I have noted cases of giardia infection which had revealed a non-filling of the gall bladder. Others have found a normal filling of the gall bladder in their studies. Hartman and his co-workers report a case of giardia infection in which the organisms were found in the gall bladder bile at operation, the cholecystogram revealed a non-filling gall bladder.

Benign tumors of the gall bladder have been recognized in increasing numbers since the advent of cholecystography. The roentgen picture is more or less characteristic of the condition. Shepard and his co-workers report 150 cases of benign tumors of the gall bladder, the majority were adenomatous. They point out that stones and chronic inflammation are often associated with these tumors. An unusual case

of varices of the gall bladder had been reported by Feldman and his co-workers, which was associated with a mucosal cyst. The X-ray revealed a characteristic picture of both conditions.

During the past year numerous contributions on biliary fistulas have appeared in the literature. The roentgenologic examination has contributed invaluable diagnostic information regarding this condition. Hicken and his co-workers reported 23 cases of external biliary fistulas. Diadrast injected into the sinus tract yielded information as to the patency of the tract and frequently the causative factor. They emphasize the causes of obstruction, namely, gall stones, blood clots, plugs of mucus, inspissated bile, pancreatitis exerting pressure on the ampulla, carcinoma and biliary dyssynergia. McCorkle and Fong report on the clinical significance of gas in the gall bladder, cite six cases, 3 being due to an anaerobic gas forming bacteria and 3 to a cholecystenteric fistula. Garland and Brown report 2 cases of choledochoduodenal fistula due to peptic ulceration. Delano reported 2 cases of internal fistula. Puestow found 16 cases of internal biliary fistula in 500 operations for biliary disease. In the majority of cases stones were found to be the cause of the common duct obstruction. The cystic duct was obstructed in 2 of the 16 cases. Internal fistulae with the passage of gall stones frequently produce intestinal obstruction. Foss and Summers report 10 cases of intestinal obstruction due to gall stones. The roentgen diagnosis is made by directly visualizing the gall stone, by the presence of air or contrast media in the biliary tract and signs of intestinal obstruction.

Functional disturbances of the common and hepatic bile ducts are rarely observed. These disturbances may interfere with the cholecystographic visualization of the gall bladder. The roentgenologic demonstration of the bile ducts by the direct instillation of an opaque medium through a drainage tube in the common duct or gall bladder is the only means of directly visualizing the functional changes that occur in the ducts and the openings. Mirizzi discusses the functional changes that occur in the duct which may be revealed as a spasm of the sphincter of Oddi, hypertrophy, hyperplasia, inflammation or stricture. Odditis is divided into dystonia and stenotic odditis. In these conditions there may be a reflux of the opaque medium into the pancreatic duct.

Cysts of the common duct are exceedingly rare. Smith found 2 cases in 757,000 case reports. The condition may not be associated with jaundice but may produce a large mass displacing the adjacent organs. It is possible however, for a large cyst to produce pressure on the common duct, which may result in jaundice. Oppenheimer reports a case of carcinoma of the cystic duct which caused common duct obstruction.

LIVER

Numerous pathologic conditions of the liver are recognized by means of the X-ray. They may be demonstrated as (1) enlargement of the liver, (2) visualization of a soft tissue tumor producing pressure upon the adjacent organs, (3) calcific processes, (4) abnormalities of position of the diaphragm, (5) presence of abscessed air cavities and (6) abnormal shadows following the use of a contrast medium. Benson and Penberthy report a case of hamartoma of the liver in which the X-ray revealed an enlargement of

the right lobe of liver with displacement of the right colon downward and mesialward. Liver abscess may occasionally be demonstrated by the visualization of the abscess cavity or by its upward protrusion producing a localized elevation of the diaphragm. A case of primary abscess of the liver due to anaerobic non-hemolytic streptococcus is reported by St John and his co-workers. Munroe reported a solitary nonparasitic cyst of the liver producing a huge sized liver displacing the adjacent organs. Hemangioma of the liver is not commonly recognized. A few cases of interest are recorded by Mouton and by Schumacker. In both instances the tumor was large in size, producing pressure upon the lesser curvature of the stomach.

Hydatid cysts of the liver are not often seen. Most of the publications appearing in the literature are case reports. The diagnosis is made by the presence of an enlarged liver in addition to the calcification of the wall of the cyst. Calcification of the cyst is very common in this condition. Two cases of echinococcal cysts are reported by Steinke, one in the left lobe of the liver, the other occurring in the spleen.

Subphrenic abscess is a condition frequently seen by the roentgenologist. The roentgenologic examination is of inestimable value in the diagnosis of this condition. The etiology is variable, is ordinarily secondary to a suppurative process elsewhere in the abdomen. Hochberg reported 139 cases, found that 44 were due to primary disease of the liver or biliary passages, 29 to the appendix, 9 to renal disease and 8 to disease of the stomach and duodenum. The roentgen signs of subphrenic abscess are lessened density beneath the diaphragm, the presence of a gas bubble, fluid level, obliteration of the costophrenic angle, fluid in the thorax, and basilar pneumonitis. Of particular interest is the roentgen signs that occur on the left side. In the erect posture there is a downward displacement of the stomach bubble. Waugh and Epstein likewise emphasize the left sided phenomenon, stressing that the separation of the cardia of the stomach on splenic flexure from the diaphragm as definite roentgenologic signs of left sided subdiaphragmatic abscess. Complications of subphrenic abscess are frequent, most of which involve the pleura and basal portions of the lung. Fistula formation however is rarely seen. A case of broncho-colic fistula following a subphrenic abscess is reported by Ackerman. The fistula may be demonstrated by means of a bronchogram or a colon enema.

Tumors of the diaphragm are comparatively rare and the diagnosis is not always made with certainty. A complete roentgen investigation is of inestimable value in the differential diagnosis. Two cases of tumor of the diaphragm were reported by Ackerman.

Fungoid infections of the gastro-intestinal tract are uncommon. Merchant stresses that in the presence of a sinus tract one should look for sulphur granules which is pathognomonic of actinomycosis. Thompson and his co-workers report a case of blastomycosis of the cecum in which the roentgen examination revealed a filling defect with a corresponding mass. Although the skin is the usual site for this disease, various systemic manifestations are recorded. There have been a few cases of widespread blastomycosis of the abdomen published. Coccidioid disease is a chronic progressive fungus disease affecting various parts of the body. Stiles and Davis report on this condition, empha-

sizing that the gastro-intestinal tract is rarely involved in this disease.

PANCREAS

Anomalous development of the pancreas is not uncommon, though rare. Aberrant pancreatic tissue may occur in various parts of the digestive tract. Smith recorded a case in which a nodule of pancreatic tissue was found in the duodenal wall. Annular pancreas is another developmental condition which ordinarily encircles the duodenum producing obstructive signs. A case is reported by Lehman which had produced a gastric retention.

The movements of the pancreas are reported by Beling and his co-workers. They report 2 cases of calcification of the pancreas which revealed variations in position in different postures. The authors show that the pancreas is a mobile organ.

Pancreatic abscess is rarely diagnosed by means of the X-ray. The roentgen signs simulate other types of tumor. Belle reported a case of pancreatic abscess in which the X-ray revealed a large pressure filling defect on the lesser curvature of the stomach.

Of extraordinary interest to the roentgenologist as well as to the gastro-enterologist are the islet cell tumors of the pancreas. Although they are ordinarily small in size and are not recognized by means of the X-ray, occasionally they may attain large size and produce signs of pressure upon the adjacent viscera. The roentgenologic examination plays an important role in the differential diagnosis of this condition, eliminating other gastro-intestinal conditions. In recent years numerous reports on this condition have been published. The number of cases have increased during the past year. Quarrier and Bingham report 4 cases. Duff states that the most frequent site of involvement is the tail of the pancreas, while 25 per cent occur in the head or at the junction of the head and body. Multiple islet cell tumors were found in 12 per cent of cases. Keirwin found 11 cases of islet cell tumors in 6,700 autopsies. He emphasized the brain changes that may occur in this condition, reporting a case with cerebral complications.

Numerous cases of cysts of the pancreas have been recorded during the past year. They may be single or multiple and generally attain a large size. Nygaard and Stacy in their report of a congenital cyst of the pancreas stress that the majority are pseudocysts. Rabinovitch and Pines report 17 cases of pancreatic cysts, 11 of which were pseudocysts, of the remaining 6 cases, 2 were cystadenomas, 2 retention cysts, 1 inclusion cyst and 1 cyst with carcinomatous changes. Poland reported a case of recurrent multilocular cyst of the pancreas. In his case the gall bladder failed to fill, following the administration of dye. Bower and his co-workers report 5 cases of cystadenoma of the pancreas, in 4 the mass in the left upper quadrant produced pressure roentgen signs. Numerous reports on carcinoma of the pancreas are recorded in this year's literature. Of particular interest are the newer surgical procedures for the relief of pancreatic disease. Russum and Crisp found 26 cases of carcinoma of the body and tail of the pancreas in 3,500 autopsies.

Calcification of the pancreas and pancreatic lithiasis are being recognized with greater frequency. Many single case reports appear in the literature. King and Waghlestein report 4 cases of calcification of the

pancreas Moss and Freis report 2 cases of pancreatic lithiasis, stress the clinical features, such as pain in upper abdomen, fatty diarrhea, enlarged liver, associated gall stones and diabetes Beling and his co-workers report a case of disseminated pancreatic lithiasis

SPLEEN

Diseases of the spleen are frequently recognized by means of the X-ray. In the differential diagnosis of splenic disease the roentgenologic examination offers valuable aid. Most of the conditions recognized by the X-ray are revealed by an enlargement of the spleen, by calcification, by pressure upon the adjacent viscera and by its effects upon distant organs, i.e. esophagus as in the case of varices. Two cases of chronic occlusion of the portal vein are reported by Bosse and Strang, one of which was associated with an aneurysm of the splenic artery. Reich reported a case of a portal phlebosclerosis involving the portal vein and its splenic branch. The condition was suspected by the splenomegaly and anemia. He pointed out that in this condition there is no ascites as is the rule in varicosities due to cirrhosis of the liver or Banti's disease. Lemmon and Paschal report a case which was demonstrated by the X-ray, of a splenic abscess producing an enlarged spleen which had displaced the colon. Pines and Rabinovitch report a case of hemangioma of the spleen, found 6 cases in 3,676 autopsies. They point out that it is the most frequent benign neoplasm of the spleen and that in none of the cases was there clinical evidence of the condition. Denneen reported 5 cases of hemorrhagic cysts of the spleen. The X-ray revealed a displacement of the stomach to the right with a smooth pressure filling defect. A case of a large solitary calcified cystic tumor of the spleen is reported by Culver and his co-workers, in which there was an elevation of the diaphragm, displacement of the stomach and colon and spreading of the ribs. Gallagher and Mossberger report a case of calcified unilocular cyst of the spleen demonstrated by the X-ray. The roentgen diagnosis of lacerated spleen is discussed by Solis-Cohen and Levine, in which they found an obliteration of the splenic shadow, signs of a hemoperitoneum resulting in a jagged serrated greater curvature of the stomach, dilatation of the stomach and tenting of the diaphragm.

ABDOMINAL VESSELS

The roentgen demonstration of changes in the abdominal vessels have been repeatedly brought to our attention. A number of interesting reports have appeared in the literature during the past year. Palmer

reported a case of marked tortuosity of the abdominal aorta which produced attacks of intestinal obstruction. The X-ray in his case showed a pressure defect of a pulsating mass on the colon. Eliason and McNamee reported 24 cases of abdominal aneurysms which they had encountered in 200,000 hospital admissions. In 16 of the cases in which the X-ray was employed 11 showed erosion of the vertebra. Groedel in a report on the differential diagnosis between abdominal aneurysms and other abdominal disease mentions the visibility of the vessel following the intravenous injection of dye, the presence of calcium deposits, displacement of the abdominal viscera and a palpable mass as aids in diagnosis. A case of aneurysm of the hepatic artery is reported by Malloy and Jason, which showed some calcification. They collected 84 cases. The condition should be suspected from the observation of calcification in the hepatic area after the elimination of other calcified shadows.

MISCELLANEOUS CONDITIONS

Mesenteric cysts may be roentgenologically demonstrated directly or indirectly by pressure which they exert upon the adjacent viscera. The cysts may reveal a calcification of the wall. Hinkel reported 3 cases of mesenteric cysts which were demonstrated by the X-ray. Kross reported 1 case of mesenteric cyst. Retroperitoneal tumors are not uncommonly seen in the roentgen examination. They are either cystic or solid. Some may be demonstrated on the roentgenogram and their posterior position aids in their recognition. Acuff discusses the various types of retroperitoneal tumors. Glandular enlargements in the abdomen are a common occurrence, but for the most part are not easily demonstrated by means of the X-ray. Only when they are large enough in size as to produce pressure upon the adjacent viscera can they be suspected. Frequently they are calcified. Poppel and Starr report an interesting case of acute infectious abdominal mononucleosis in which the X-ray revealed evidence of pressure upon the duodenum, caused by the enlarged glands.

The 1942 literature contains numerous publications which contribute important information regarding diseases of the digestive tract. Many interesting and illuminating facts and much of statistical value pertaining to gastro-intestinal diseases are presented. Numerous case reports of unusual cases are recorded. This accumulated review of the year's literature makes it possible for one to briefly scan over the important contributions of what is new in the field of digestive diseases.

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The Influence of Vitamin C on Wassermann Fastness in Syphilis

By

SIMON L. RUSKIN, MD
NEW YORK, NEW YORK

THE economic importance of Wassermann fastness has assumed proportions of serious magnitude for the nation at war. Every possible factor influencing Wassermann fastness is deserving of the most careful consideration.

It is not unnatural that Vitamin C should offer such promising possibilities in this problem since at the very outset of antiluetic treatment, Ehrlich indicated that reduction played a most significant part in the toxicity and effectiveness of arsphenamine. Today we know more about the redox mechanisms that exercise so great an influence on the reduction and oxidation processes of the body. Chief among these redox agents is of course, Ascorbic Acid.

What is perhaps most important is that not only does the animal body require this substance, but as Klingler, Guggenheim and also Farber have shown some bacteria utilize it while other organisms such as pertussis and trypanosomes may be destroyed in vitro by Vitamin C. The possibility therefore exists of using

ascorbic acid in some instances to increase the absorption of bactericidal agents and in other cases to take advantage of the direct lethal action as well.

However in studying such redox substances as ascorbic acid, one can use the analogous data accumulated with another collateral redox substance, glutathione. It must be observed that arsenic and antimony while they are detoxified by reducing substances are made more toxic by oxidizing agents. Danow has shown that arsphenamine that has been allowed to oxidize is far more toxic than when kept in the reduced state. So potent an influence do the reducing properties play on diminishing toxicity of arsenic and antimony that it has been designated as an interference mechanism and Janoso has formulated a classification of a number of drugs that fall between 0.115% and 0.60% of the oxidation reduction scale at pH 7 which show strong interference action. He describes Vitamin C as having strong interference action towards antimony. In these calculations, he

does not take into account that while in the reduced state, the detoxifying action of arsenic or antimony is most pronounced, yet in the normal metabolism of these oxidation-reduction agents, the oxidized state rapidly supervenes and it is in that condition that the therapeutic effect is attained.

In this study, bismuth cevitamate was employed and interesting reversals were obtained in a series of Wassermann fast cases. Bundesen, et al, have shown that Vitamin C would markedly diminish the toxicity of arsphenamine not only for administration, but also for the skin test in arsenic sensitive patients. The increased therapeutic activity of the metabolized bismuth cevitamate would point to the change in toxicity incident to the oxidized state of the cevitamate.

This was further borne out by experimental data showing that Janesco's conclusions drawn only to the reduced state of a redox substance are incomplete. In a comparative study of the maximum tolerated dose per kilogram, the following values were obtained with rabbits:

	Maximum Tolerated Dose Per Kg	Therapeutic Index
Solaelum Bismuth Tartrate (Aqueous)	0.066 Gm	15.1
Bismuth Subsalicylate	0.006 Gm	10.4
Bismo—C ₃ mol	0.060 to 0.080 Gm	16.6-12.5
Bismo—Laurin	0.080 Gm	12.5
Potassium Bismuth Tartrate (oil suspension)	0.070 Gm	12.5
Bismuth Cevitamate	0.030 Gm	33.3

Although the maximum tolerated dose was lowest, yet by the same token, its therapeutic index was highest since the toxicity for the organism exists in the same ratio as for the host. The tolerance of the host is, of course, far greater than that of the spirochete. Clinically, it also worked out in the same manner, and therapeutically the bismuth cevitamate proved gratifying.

Study of another member of the redox system, glutathione and cystine shows quite a parallel relationship to arsenic and trypanosomes. Singer and Fischl showed that cystine in the oxidized form gave a strong increase of trypanocidal action of atoxyl, whereas cystine in the reduced form did not. They showed that spirochetes and trypanosomes take up considerable quantities of arsenic and gold compounds not only in vivo, but also in vitro. At the same time, it was demonstrated that after being one hour in atoxyl solution at a concentration of 1-1000, neither the trypanosomes nor spirochetes showed a diminution of its infectivity. On the other hand, atoxyl digested with liver extract had a deleterious effect on trypanosomes. In liver extract they point out there is

present in addition to cystine, a rich supply of glutathione and glycogen.

Another factor of interest is their observation that liver extract increased the ability of various substrates to take up more atoxyl—thus animal charcoal, colloidal, erythrocytes and proteus bacteria took up considerably more arsenic out of the solution with liver extract than from the pure solution of atoxyl. Subsequent experiments showed that in vitro atoxyl plus cystine of glutathione had a definitely greater trypanocidal action than atoxyl alone. The glutathione plus atoxyl prevented the infectivity of Nagana which did not occur with atoxyl alone. The atoxyl glutathione complex was even more active than the atoxyl liver extract, thus showing that the oxidation-reduction mechanism of the glutathione was involved in the enhanced trypanocidal action. We could thus correlate the observation of Voegtlin that glutathione in the reduced state had an inhibiting or interference action on arsenic, whereas when digested with atoxyl solution in the oxidized form, it had an enhancing action on the trypanocidal action of atoxyl.

Still another interesting group of experiments were conducted by Singer and Fischl to study the effects of redox systems such as glutathione and Vitamin C. A summary of their findings is demonstrated by their Table III.

The effect of glutathione and ascorbic acid with and without chemotherapeutic agents on the infecting organisms in vitro.

The plus marks indicate the severity of the infection after one hour incubation in the solution from which 0.1 cc was used to infect mice intraperitoneally.

From these experiments Singer and Fischl state it was amazing to find that ascorbic acid in a concentration of 1-800, after one hour stay in the test tube could kill trypanosomes while spirochetes were uninfluenced. However our clinical experience would seem to show that in vivo the bismuth cevitamate had a unique and striking action on spirochaetal infection particularly in the Wassermann fast syphilis. Further it was evident to these investigators that between atoxyl and ascorbic acid apparently a chemical reaction occurred since the solution resulting from these components had a destructive action on the trypanosomes while individually they were unable to kill all organisms. Likewise the mixture of ascorbic acid with the relatively innocuous thiourea was entirely lethal. With spirochete similar experiments in vitro did not give the same results.

The classical summing up of Singer and Fischl, both of whom may be considered as among the outstanding chemotherapeutic investigators of the time, casts an interesting light on the whole subject. They state "Precisely these experiments show how incorrect hasty generalizations can be in these complicated problems and it seems somewhat difficult to

	Atoxyl 1-1000			Thiourea 1-1000			Glutathione 1-500	Ascorbic Acid 1-500
	Without Addition	With Glutathione	With Ascorbic Acid	Without Addition	With Glutathione	With Ascorbic Acid		
Recurrents	+	+	+	+	+	+	+	+
Nagana	+	+	+	+	+	+	+	+

draw far reaching conclusions, more or less because of this aspect of the problem, that the body has within it the reducing substance, glutathione specific for trypanocidal action and ascorbic acid as specific for spirocheticidal action. We are more inclined to believe as a result of these afordescribed experiments that the effects of chemicals in vitro are not necessarily the same as in vivo. In chemotherapy the situation is obviously quite different from that, for example, in Vitamin research. They conclude with the remarks, "We have temporarily refrained from further investigations of these phenomena, since only a practical investigation of chemotherapeutic action in vivo is able to give greater elucidation and such series of investigations is not to be hoped for in the present state of knowledge."

Fortunately in the study of Wassermann fast syphilis, we have for the first time the necessary means for conducting such investigations of which Singer and Fischl despaired. The conversion of Wassermann fast cases that had resisted other combinations of Bismuth and Arspenamine but responded to Bismuth Cevitamate or Bismuth Cevitamate and Arspenamine, give a striking proof of the spirocheticidal action of the ascorbic radical in vivo. Another fortunate contribution in the research of this problem has been the development by Dr. Raymond Jonnard of an improvement in the interferential refractometer permitting the reading of two decimal points farther than the Abbe refractometer. It has been shown by numerous investigators, particularly Pick of the Vienna school that substances injected into the circulation can be utilized only if they tend to form serum protein complexes. Failure for such complexes to form results in the inability on the part of the body to utilize the product with a resultant toxic reaction.

By the use of the interferential refractometer of Jonnard, one can readily demonstrate a specific minimum of refraction when a substance added to the blood serum reacts chemically with serum proteins. Jonnard has suggested and demonstrated that substances causing allergic reactions, such as aspirin fail in those individuals to react with the serum proteins and do not give the characteristic curve.

This peculiarity in serum protein behavior possibly accounts for the reactions occurring to Arsenic and Bismuth Compounds. Such variations should be possible of determination by Jonnard's technique of interferential refractometry. One such case of reaction to Bismuth Cevitamate was observed in the clinical series of cases here reported and demonstrates again the significance of the biochemical factor independent of the question of therapeutic responses. A series of readings made by Dr. Jonnard demonstrated the protein complex formation of Bismuth Cevitamate and Bismuth Glutathione with serum protein.

The interferential refractometric method showed the reaction of Bismuth Cevitamate with serum proteins to be complete at the following amounts:

Serum number—	BH 12788	0.5 mgs per cc serum
"	" BH 12778	0.2
"	" BH 12799	0.1 (doubtful)
"	" BH 12791	0.3
"	" BH 12792	0.2
"	" BH 12794	0.2
"	" BH 12795	no reaction

These reactions would indicate that the combining powers of Bismuth Cevitamate would range between 10 to 50 mg per 100 cc of serum. The variations in combining property or the absence of protein complex formation also explains the individual idiosyncrasies, one of which occurred in the series here reported.

The mechanism of the toxicologic action of bismuth in the treatment of syphilis was described by Kolmer. He states that "the toxicity of the various organic and inorganic compounds of bismuth advocated and employed in the treatment of syphilis apparently depends upon the dissociated ions of bismuth itself. In general terms it would appear that the toxicity of various bismuth preparations bears a relation to the amount of bismuth and this would be true if the compounds were equally soluble in the tissue fluids and if the bismuth ions were dissociated with equal rapidity from the different compounds. A full complex compound may contain more mercury than a half or pseudo complex compound and yet prove less toxic (and likewise less therapeutic). The same principles cover the toxicity of bismuth compounds for both the host (organo-tropism) and the parasites (parasitotropism)."

An analysis therefore of all the factors involved in the unique clinical results here reported would tend to show that a combination of favorable properties is involved, first its relationship to the oxidation reduction mechanism and the ability of cevitamate acid to be trypanosomicidal, second, its readiness to form serum protein complexes, third, its solubility and ready absorbability, fourth, the high therapeutic index. The combination of these factors apparently holds an important key to the problem of Wassermann fastness.

The clinical studies here reported were conducted by Dr. Miron Silberstein. The results indicate a possible avenue for further progress in a field that today has assumed such a vital role. Though the series here reported is very limited, nevertheless the Wassermann reaction is a laboratory record free from subjective clinical conclusion and a small series of such records is of more scientific value than a large series of clinical impressions.

In this report only Bismuth Cevitamate is considered.

CASE REPORTS

Case 1. Mr. P. M. history of lues for the last four years. He received administration of combined treatment of neo-arsphenamine and mercury for the same period of time, but it would not change Wassermann test to negative. His last Wassermann test in February, 1938, was 4 plus. Administration of Bismuth Cevitamate twice weekly for five weeks. Wassermann test rechecked and reply came back for first time, plus minus. His subjective condition was markedly improved, and the patient insisted on continuation of the same treatment. He received ten more injections, that is twenty injections without interruption and without any untoward objective or subjective symptoms.

Case 2. Mrs. H. W. history of lues since May of 1937. Wassermann results in June, 1937, was 4 plus. Received a course of anti-luetic treatment, consisting of ten neo-arsphenamine and ten soluble Bismuth injections. Treatment was continued until January, 1938, when Wassermann test showed 3 plus reaction. She was then placed on combined neo-arsphenamine and Bismuth Cevitamate treatment. Wassermann test taken on April 28, 1938, showed negative reaction.

Case 3. Mr. J. M. history of lues of eight years' duration for which he received combined treatment until

February, 1938. He came under my observation on December, 1934. Wassermann results in December, 1934, were 3 plus. Wassermann reports remained continuously positive, the last one in February, 1938, showed 3 plus. He received since that time Bismuth Cevitamate treatment. On May 5, 1938, Wassermann test showed negative reaction.

Case 4. Mr. L. C. history of lues since October, 1934, at which time Wassermann test showed 4 plus. He received continuous treatment of neo-arsphenamine and soluble Bismuth injections until December, 1937, without any change in Wassermann reaction. Patient was put on combined treatment of neo-arsphenamine and Bismuth Cevitamate. He received ten of each injections until March, 1938. Wassermann taken on May 3, 1938, reports negative results.

Case 5. Mr. O. C. history of lues since 1931. Received treatment of neoarsphenamine and soluble Bismuth and Mercur. Wassermann test at no time below 4 plus. On February 22, 1938, was put on Bismuth Cevitamate treatment alone. After ten intramuscular injections, Wassermann was taken and showed a 4 plus. It is interesting to note at this time that the patient reacted very badly to these injections. He claims he felt nausea, chills and general debility the whole day after injection and refused to continue treatment.

Case 6. Mr. F. C. history of Ulcus Durus with Wassermann report of 4 plus. Continuous treatment of neoarsphenamine and soluble Bismuth of eight months' duration did not change Wassermann which remained 4 plus. The patient was put on neoarsphenamine and Bismuth Cevitamate, alternating injections for two and a half months' duration. Wassermann reaction after that showed report 1 plus. At the present time, patient is still under treatment with Bismuth Cevitamate.

Case 7. Mr. A. G. came to my office in January, 1936, with symptoms of severe pain in both legs and very severe headaches, mostly on the left side of the head. His Wassermann at the time was 4 plus. I did not make a careful physical examination but I had the impression he was suffering from cerebral gumma and osteomyelitis luetica. His disease was of long standing, and he has received varied treatment at different times until he came to my office in 1936. At this time he was put on neoarsphenamine and bismuth. Wassermann reaction was 3 plus and

4 plus. In the early part of January, 1938, he was put on combined Bismuth Cevitamate and neoarsphenamine, a total of twenty injections each administered bi-weekly, and on May 16, 1938, Wassermann test came back negative. Pain in both legs and headaches disappeared and subjectively he felt absolutely normal.

Case 8. Mr. F. C. presented a history of Ulcus Durus. Wassermann test was taken in April, 1936, with results of 4 plus. He was treated with bi-weekly injections of soluble Bismuth and neoarsphenamine and was treated with intermissions until January, 1938. His Wassermann was still 3 plus. Simultaneously, he was treated for acute gonorrhea from which he was discharged in January, 1938. At this time, he was put on Bismuth Cevitamate and neoarsphenamine. Received twenty injections of each bi-weekly. Wassermann taken June, 1938, came back negative.

Case 9. Miss G. G. Dancer, came to my office on March 11, 1938, with complaints of a sore throat. Careful examination revealed two chancroids on each side of the lower lip and typical luetic angina. Wassermann was taken and then came back on March 16th, 4 plus. She was put at once on Bismuth Cevitamate and neoarsphenamine treatment. Seventeen injections of each were given bi-weekly. On June 17th, Wassermann came back negative. It is worthwhile to notice that luetic symptoms which were found at the very first visit disappeared immediately after two Bismuth Cevitamate injections.

Case 10. Mr. C. C., male, 30 years old, history of lues since September, 1935. Examination revealed pustulous erythematous eruptions all over the body. Last exposure as far as the patient can remember January, 1935. Wassermann examination which was taken on the day of admission revealed 4 plus reaction. In March, 1936, Wassermann reaction was 3 plus, after bi-weekly injections of Neo-salvarsan and Bismuth. Specific treatment was continued and at the end of the same year showed 4 plus reaction. At the end of 1936, Wassermann reaction again showed 3 plus, after which the patient was put on Bismuth Cevitamate intramuscular injections, twice weekly. On August, 1936, Wassermann was taken with negative results. Subjective condition of the patient was excellent. Injections of Bismuth Cevitamate were taken without any local pain or general physical disturbance.

A tabulation of the results is as follows:

Case	Duration of Lues	Previous Therapy	Previous Wassermann After Therapy	Bismuth Cevitamate Alone	Bismuth Cevitamate Combined with Neo-Arsph	Result
1	4 yrs	Neo-Arsph and Mercury	4 plus	Twice weekly 5 weeks 10 more injections		Plus Minus
2	1 yr	Neo-Arsph and Sol Bismuth	3 plus		Jan to Apr Neo-Arsph & Bismuth Cevitamate	Negative
3	8 yrs		3 plus	Feb to May Bismuth Cevitamate		Negative
4	4 yrs	Neo-Arsph and Sol Bismuth	4 plus		Neo-Arsph and Bis Cev 10 each	Negative
5	7 yrs	Neo-Arsph and Sol Bismuth Mercury	4 plus	10 injections		Reaction Nausea chilliness
6	8 mos	Neo-Arsph and Sol Bismuth	4 plus		2½ mos Alternate Bis Cev and Neo-Arsph	Plus one
7	Old tertiary	Neo-Arsph and Bismuth	3 plus 4 plus		Bismuth Cev and Neo-Arsph Jan to May 20 inj—each bi-weekly	Negative
8	2 yrs	Varied till 1936 Neo-Arsph and Sol Bismuth	3 plus		Bismuth Cev and Neo-Arsph 20 inj each bi-weekly Jan 1938	Negative
9	Recent	None	4 plus		Bismuth Cev and Neo-Arsph 17 injections	Negative Initial lesion disappeared after 2 inj Bismuth Cevitamate
10	3 yrs	Neo-Arsph and Bismuth Sept. 1935 to Dec 1937	3 plus 4 plus	Bismuth Cevitamate twice weekly Jan to Aug 1938 with intervals 30 inj in all		Negative

CONCLUSION

1 Vitamin C apparently enhances the spirocheticidal effect of bismuth and the trypanosomicidal effect of antimony.

2 Wassermann fastness is related not only to the mechanism of inhibitors, but also to the chemotherapeutic index of the bismuth preparation employed.

With all other factors equal, the addition of the use of Bismuth Cevitamate was able to change the Wassermann fast positive to Wassermann negative in seven Wassermann fast cases out of the series of ten luetics.

3 Vitamin C and glutathione influence the capacity for spirochaetes and trypanosomes to take up Arsenic, Antimony, Bismuth and Gold.

4 Vitamin C acts both as a detoxifier of Antimony, Arsenic and Bismuth in the reduced state but can enhance the spirochetal and trypanosomal action of these metals during the process of oxidation.

5 Bismuth Cevitamate may be considered an important addition to the therapy of Wassermann fast luetic.

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The Absorption of Vitamin A in Chronic Ulcerative Colitis*

By

ROBERT C PAGE, M D
and
Z. BERCOVITZ, M D
NEW YORK NEW YORK

MALNUTRITION and underweight usually are present in persons with idiopathic chronic ulcerative colitis. In the chronic phase of this disease, the patient often has an adequate intake of food but does not gain weight. Therefore, it would appear that there

is an interference with absorption in the small intestine. In a previous study, we reported (1) an incidence of 24.2% of patients with chronic ulcerative colitis who had Vitamin A levels below 10 Blue Units per 100 ml of plasma. This suggested that patients with this syndrome should be investigated by means of the Vitamin A absorption test. The following ex-

*From the Gastro-Enterology Clinic, Department of Medicine, New York Post Graduate Medical School and Hospital.

periment was therefore carried out to study the absorption of Vitamin A by determining its level in the blood plasma before and after the oral administration of 100,000 U S P units of Vitamin A

METHOD OF STUDY

Vitamin A and carotenoid content of the fasting blood plasma was determined in 25 patients with chronic ulcerative colitis, 9 patients with miscellaneous

TABLE I

Data of Vitamin A tolerance tests which consisted in the oral administration of 100,000 U S P units of Vitamin A in the form of a fish oil concentrate to each patient. Blood samples were taken before administration of the Vitamin A and at 2, 4, 6 and 24-hour intervals, following its administration

PLASMA CAROTENOIDS (Units %)							PLASMA VITAMIN A (Blue Units %)				
CHRONIC ULCERATIVE COLITIS											
Case No	No BM **	Control	2-Hr	4 Hr	6 Hr	24 Hr	Control	2 Hr	4 Hr	6 Hr	24 Hr
1	2	55 units	38	04	141	123	20	20	125	75	13
2	3-6	100	107	117	200	101	18	20	150	70	40
3	*	08	04	04		104	10	23	00		13
4	1 3	08	115	120	130	103	25	80	125	75	30
5	5-8	70	82	80	81		13	25	85	60	
6	10 15	98	83	66	04	56	20	25	75	50	15
7	1-2	104	102	124	86	108	8	12	75	20	10
8	6 0	72	82	03	79	82	10	15	75	30	15
9	1	113	110	97	112	144	20	30	50	75	75
10	10	42	43	46	40	57	10	10	30	25	12
11	0 1	123	06	170	140	123	30	50	200	100	40
12	5-6	110	115	80	125		20	20	40	50	
13	1	87	08	05	02	88	8	30	200	75	10
14	8 10	38	42	57	86	97	15	15	75	40	13
15	7-8	102	203	156	214	107	10	20	100	75	12
16	1 2	220	107	234	230	100	25	50	175	75	30
17	0 7	103	123	150	150	221	18	50	55	40	18
18	2 3	92	187	51	147	112	15	25	75	50	20
19	0 8	44	42	43	50	91	12	20	30	30	25
20	4 8	08	87	01	77	80	12	20	100	75	20
21	6-8	130	75	71	145	115	18	10	35	100	15
22	1 3	221	221	205	234	300	30	40	00	125	30
23	10 15	59	62	00	72	57	8	10	20	30	12
24	2 3	117	117	82	81	100	15	25	50	50	15
25	0 7	45	44	43	42	125	13	23	00	125	25
Average		101.0	102.5	101.6	120.3	121.2	15.1	24.7	89.4	64.6	22.1
NORMALS											
26	1	121	150	121	134	153	25	30	150	225	25
27	1	110	178	123	141	170	18	25	100	75	20
28	1	86	80	72	82	96	18	30	100	75	15
29	1	155	143	250	143	150	23	80	150	75	23
30	1	88	08	101	87	81	15	25	150	25	25
31	1	101	121	70	04	121	15	20	30	125	175
32	1	158	155	121	134	153	20	25	175	100	20
33	1	132	115	144	136	139	13	40	150	75	13
Average		110.5	132.4	125.3	118.0	135.3	18.4	34.4	125.6	66.9	39.6
MISCELLANEOUS											
Amoebic Dysentery											
34	1 2	104	120	101	174	106	12	15	50	50	25
Gastritis											
35	1 2	76	147	134	198	75	13	25	50	60	15
Hepatitis											
36	1-2	49	45	43	48	46	20	30	50	40	18
Lymphogranuloma Venereum											
37	8-10	94	115	123	125	140	15	25	125	30	15
Nutritional Deficiency											
38	2 3	40	47	45	53	50	5	10	13	40	40
Spastic Colitis											
39	5 10	114	224	135	174	167	15	50	150	80	20
40	4 5	00	92	01	101	92	15	25	100	125	25
41	2 3	95	130	131	130	106	20	30	200	75	25
42	0 1	100	147	187	130	147	13	25	150	100	15
Average		85.7	119.6	110.1	126.9	110	14.2	25.1	99.8	66.7	22

*Ileostomy

**Average number of daily bowel movements

diseases of the gastro-intestinal tract and 8 healthy, normal adults as controls

Immediately after taking the fasting blood sample, each subject was given orally 100,000 U.S.P. units of Vitamin A in the form of a fish oil concentrate. Blood samples were then taken at 2, 4, 6 and 24 hour intervals. Food low in Vitamin A and fat was allowed to be taken in small quantity for 24 hours, e.g. dry toast, fruit juices and tea. This was considered to be necessary in order that Vitamin A and fats in foods that might influence absorption would be at a minimum, and thus the blood level would be as nearly as possible a true expression of the absorptive ability for Vitamin A of the gastro-intestinal tract.

The method employed for Vitamin A was the modified Price-Carr antimony trichloride reaction (Clausen and McCoord (2)). The normal limits of the plasma Vitamin A level by this method are 10 to 20 Blue Units per 100 cc.

Carotenes and xanthophylls are known to be precursors of Vitamin A; therefore a study of the carote-

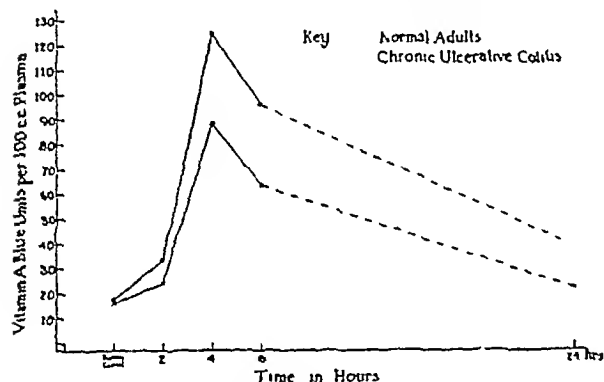


Fig. 1 Graph showing mean plasma levels of Vitamin A in 8 normal adults and 25 patients with chronic ulcerative colitis, both fasting and at intervals, following oral ingestion of 100,000 U.S.P. units of Vitamin A in fish oil concentrate.

noid content of the blood was carried out in conjunction with the Vitamin A studies. The plasma carotenoids were determined by the modified Price-Carr antimony trichloride reaction (2) by measuring the intensity of the yellow color of the petroleum ether plasma extract. The normal range by this method is 50-100 units per 100 cc.

RESULT OF STUDY

The Vitamin A absorption test was performed in 25 patients with chronic ulcerative colitis. Only three patients had a low fasting plasma Vitamin A level (below 10 Blue Units per cent) and the mean for the group was 16.1 Blue Units. Two hours after the oral administration of 100,000 U.S.P. units of Vitamin A the mean plasma level had risen to 24.7 Blue Units, in 4 hours to 89.4 Blue Units, in 6 hours to 64.6 Blue Units and in 24 hours to 22.1 Blue Units (Fig. 1).

The mean fasting plasma Vitamin A level in the eight healthy, supposedly normal adults was 18.4 Blue Units and 2 hours after the test dose of Vitamin A was 34.4 Blue Units, 4 hours 125.6 Blue Units, 6

hours 96.9 Blue Units and in 24 hours was 39.5 Blue Units (Fig. 1).

The data of the patients with miscellaneous gastro-intestinal tract disturbances are given in detail in Table I.

Plasma carotenoid levels were determined on all the patients studied both before and after the ingestion of the Vitamin A. There was in general a slight increase in plasma carotenoid level after 24 hours in all patients studied (Table I).

In the patients with chronic ulcerative colitis the 4 hour mean maximal rise in plasma Vitamin A was 73.3 units higher than the fasting level while in the normal controls the mean rise was 107.2 units, thus the mean maximal rise in plasma Vitamin A at the 4 hour period in the normal controls was 46.2% greater than in the chronic ulcerative colitis patients.

The average number of daily bowel movements of the subjects studied is included in the data (Table I).

DISCUSSION

From the data obtained in this study it appears that the plasma Vitamin A level does not rise as high after an oral dose of 100,000 U.S.P. units of Vitamin A in patients with chronic ulcerative colitis as in control subjects. This would indicate that either there is an impairment of absorptive power in the intestinal tract or that there is a subnormal amount of Vitamin A stored in the liver and the Vitamin A absorbed is rapidly taken from the blood and stored in the liver so that the rise of Vitamin A in the plasma is not marked at any time.

The relationship between plasma Vitamin A levels to actual deficiency states is not clear. It is generally accepted that plasma Vitamin A level bears no direct relation to body stores and the only conclusion can be that a high blood level is inconsistent with a deficiency state (Josephs, Baber and Conn (3)). The deposits of Vitamin A protect against a reduction of blood level, so that only when the deficiency condition is at its maximum is the plasma Vitamin A likely to be markedly reduced in the absence of pathological conditions. If the preceding statements are accepted then it is probable that body stores of Vitamin A were depleted in only 3 of the 25 patients with chronic ulcerative colitis studied since in only 3 patients were the fasting Vitamin A plasma levels below 10 Blue Units per cent. Thus, it would appear that the difference between the plasma level after the test dose of Vitamin A in the chronic ulcerative colitis patients and in the control group can best be explained by decreased absorption from the intestinal tract in the patients with chronic ulcerative colitis.

The average number of daily bowel movements should be considered in evaluating absorption as it is well known that diarrhea diminishes absorption of thiamine from the intestinal tract (Dann and Cowgill (4)). Of the 24 patients with chronic ulcerative colitis in which the number of daily bowel movements were recorded, 10 had 3 or less daily and 6 of the 10 had a maximal rise of plasma Vitamin A to 100 or more Blue Units per cent following the test dose. Fourteen patients had 4 or more daily bowel movements and of these 9 had a maximal rise to less than 100 Blue Units.

per cent These data tend to indicate that there is diminished absorption of Vitamin A in the presence of an increased number of daily bowel movements

SUMMARY AND CONCLUSIONS

Vitamin A absorption tests consisting of the oral administration of 100,000 USP units of Vitamin A were carried out in 25 patients with chronic ulcerative colitis, nine patients with miscellaneous diseases of the gastro-intestinal tract and in eight healthy normal adults

The plasma Vitamin A level did not rise as high in the patients with chronic ulcerative colitis as in the

control subjects This difference can best be explained by decreased absorption

It is suggested that there may be a reflex mechanism operating from the damaged colon that inhibits absorption from the small intestine with an additional factor of diarrhea often present

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The Diet in Diabetes Mellitus*

By

WINDSOR C CUTTING, M D

and

G B ROBSON, M D

SAN FRANCISCO CALIFORNIA

DIET has always been a fundamental measure in the treatment of diabetes mellitus In the days before insulin, it was the only important means of maintaining health in a diabetic In those days it took the form of diastolic limitation of foods, especially carbohydrates Following the introduction of insulin it became possible to use diets of a higher caloric value which were adequate to maintain normal body weight However, the tendency to use diets low in carbohydrate persisted for many years, partly as a hold-over from pre-insulin days and partly because of a reluctance to use large doses of insulin

At present, with the general availability of insulin, diets containing about as much (perhaps 2/3 as much, on the average) carbohydrate as the ordinary non-diabetic diets are in wide use This makes a more palatable menu, and very likely is less conducive to such changes as arteriosclerosis, than the high fat diet It also means that the physician's or dietitian's work is decreased, in that abnormal food mixtures do not have to be prescribed or prepared

The further step to an unlimited or "free" diet, which has been advocated by certain physicians who believe that the only necessary requirement in diabetes is an adequate amount of carbohydrate be burned, has not met ready acceptance While this may rarely be permissible in persons unwilling or unable to follow a prescribed diet (except in clinics where the problem is being especially studied) it seems unwise to upset so decidedly the normal physiological state in the ordinary patient, who is quite willing to follow a diet closely

From this it follows that the diabetic should take a diet approximately like that which he naturally desires and eats It may, however, need correction in total amount, and if insulin is given, it must not vary in essential components from day to day, to prevent the

occurrence of insulin reactions If the natural diet is improper in other respects, these also must obviously be corrected The diabetic diet, then, should be consistent with the following aims (1) to make the constituents of the diet those foods which the patient usually eats, (2) to keep the total calories, carbohydrate, protein and fat relatively constant from day to day, and (3) to correct any defects which may appear in the patient's accustomed diet With these aims in mind, the diabetic diet should be constructed by the physician about as follows, this procedure being that adapted in the Stanford Metabolic Clinic

TOTAL CALORIES

The total calories should be such that the patient becomes normal in body weight If he is already at this weight, it may be maintained by 1500 calories daily, or more, depending upon his activities Although 1500 calories represents about 25 calories per kilogram of body weight for an average person, and this is generally supposed to be adequate only for basal (resting) needs, nevertheless many sedentary persons will maintain their weight on about this quantity of food Persons working vigorously need up to twice this amount, or even more, and appropriately increased diets should be prescribed

If the patient is underweight, he should be given a diet of more than average quantity Thus, 2000 or 2500 calories may allow him to gain to a proper weight, after which the diet must be somewhat reduced to prevent obesity Needless to say, diabetics, who are underweight and glycosuric, require immediate insulin therapy

If the patient is obese, he should be placed on a reducing diet As he loses weight, his carbohydrate tolerance will rapidly improve Thus many patients, mildly diabetic when overweight, are sugar-free when at normal body weight A diet containing about 1000 calories is far enough below the minimal requirements for almost any adult, to cause a steady loss of weight

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From the Departments of Pharmacology and Therapeutics and of Medicine Stanford University School of Medicine San Francisco Calif

Obese diabetic patients should not be given insulin unless they are having serious symptoms such as polydipsia or frequent nocturia, because the sugar wasted in the urine increases the rapidity with which they lose weight. If they are still glycosuric when a normal weight is reached, insulin should be given.

GRAMS OF PROTEIN

After deciding on the total caloric requirement for the diet, the amount of protein should be determined. Ordinarily this is 1 gm. of protein for every kilogram of body weight, or more simply 75 gm. of protein for an average adult. This adequately provides for tissue repair. Since 1 gm. of protein liberates 4 calories, the 75-gram allowance furnishes 300 calories.

GRAMS OF CARBOHYDRATE AND FAT

The remaining caloric requirements, after the amount of protein has been determined, are made up of carbohydrate and fat. Most persons eat by choice about twice as many grams of carbohydrate as of fat. In this mixture each type of food furnishes about an equal number of calories, as 1 gm. of carbohydrate provides 4 calories, and 1 gm. of fat furnishes 9 calories.

EXAMPLE OF A DIET FOR A DIABETIC PATIENT

If a diet of 2000 calories is desired for a patient of correct body weight doing light work, 300 calories should come from protein (or 75 gm.) leaving 1700 calories to come from carbohydrate and fat. One-half of this, or 850 calories, may come from carbohydrate (212 gm.) and one-half from fat (95 gm.). The diet prescription made out by the physician then becomes: calories 2000, protein 75 gm., carbohydrate, 212 gm., and fat, 95 gm.

Once the physician has written this prescription he may be fortunate enough to have a dietitian translate it into exactly what foods and how much of each to be eaten for the 3 meals a day, and to insure an adequate vitamin and mineral content. While the dietitian does this easily, few physicians can do so in the time available. For the majority of busy practitioners the only satisfactory solution is to lend the patient a diet list so prepared as to allow the latitude of choice of foods necessary to prevent monotony. Only a few patients become in any sense dietitians and able to construct their own menus entirely. This means that almost all diet prescriptions must fall into a very few standard types to avoid a great multiplicity of forms. It is surprising how few such "standardized" diet lists may suffice. The appended diets for about 1000, 1500, 2000 and 2500 calories have been found by us to be satisfactory in practice. These may be mimeographed, and small changes and interpolations made if necessary.

When other diseases complicate diabetes the diabetic diet should be adapted to meet any other special requirements. That is, if a patient has a peptic ulcer and a smooth diet is advisable, rough foods in the diabetic diet should be purged, or otherwise suitably prepared. If the diabetic also is tuberculous and a high caloric intake is desirable the diabetic diet is correspondingly increased. If he has nephritis and

should be given only a limited protein intake, the diabetic diet is altered accordingly.

CONCLUSION

Most diabetic patients require a quantitative diet, but this need not be greatly different from that which normal persons eat. Highly concentrated carbohydrate food is inadvisable, because a slight error in amount may make a great difference in caloric content of the diet, and because there may replace foods rich in vitamin and mineral. The use of a few standard diet forms with inherent flexibility to allow adequate choice of individual foods makes diet prescribing simple for the physician. Actual examples of such diets in practical use are presented in the appendix to this article.

APPENDIX

Sample diet forms for 1000, 1500, 2000 and 2500 calories, suitable for diabetics.

I. Reducing Diet 900 Calories

Carbohydrate 80 Gm. Protein 70 Gm. Fat 20 Gm.
Bread fast

Fruit—1 serving, Cereal—1 tablespoon (dry measure before cooking) Bread—1 slice, Egg—1 (small or medium) standard measuring cup (or canned milk $\frac{1}{2}$ cup), Butter—1 square

Lunch
Lean meat, fish or fowl—1 small serving, or cheese—1 small slice, or cottage cheese—2 heaping tablespoons, or eggs—2, Vegetables—2 generous servings (2 cups), Skim milk—1 standard measuring cup (or 1 cup 1% term M. Fat)—1 serving

Supper
Lean meat, fish or fowl—1 medium serving ($\frac{1}{2}$ pound) or cheese—2 oz. ($\frac{1}{4}$ pound), Vegetables—2 generous servings, Fruit—1 serving

One serving fruit: 1 grapefruit, 1 orange, 1 cup berries, $\frac{1}{2}$ cup watermelon (serves), $\frac{1}{2}$ small cantaloupe, 1 pear, 1 peach, 1 apricot, 2 plums, 1 small apple, 1 small banana, $\frac{1}{2}$ cup orange juice, or $\frac{1}{2}$ cup pineapple juice, 1 cup tomato juice or 1 cup grapefruit juice, or $\frac{1}{2}$ cup dried stewed apricots, or $\frac{1}{2}$ cup dried stewed prunes (dried without sugar)

Non-fat: Clear soup, plum tea or coffee with sugar meal, Saccharin ($\frac{1}{4}$ grain) may be used for sweetening, if desired. Liquid petrolatum (mineral oil) may be used to replace fats and oils as in salad dressing.

As used: Bread in any form except as stated above including gluten bread, malt toast, crackers, Pyrex krap and all certified "reducing breads."

Starchy foods: Rice, noodles, potatoes, beans, corn, peas, Sweets: Honey, jam, candy and all desserts.

Sweet fruits: Prunes, grapes, persimmons, cherries, etc., and all fruits canned with sugar.

Fats: Greasy salad dressing, mayonnaise, oil, cream, butter, hard avocado.

1 vitamin capsules (polyvalent) daily as prescribed (usually 2).

II. Diet 1500 Calories

Carbohydrate 170 Gm. Protein 75 Gm. Fat 70 Gm.
Bread fast

Fruit—1 serving, Cereal—1 tablespoon (dry measure before cooking) Milk—1 standard measuring cup or $\frac{1}{2}$ cup canned milk) Bread—1 slice, Butter—1 square, Egg—1

Lunch

Lean meat, fish or fowl—1 small slice (1 oz.) or cheese—1 small slice or cottage cheese—2 heaping tablespoons, or eggs—1, Vegetables (raw or cooked)—2 generous servings (2 cups) Fruit—1 serving, Bread—1 slice

Butter—1 square, or mayonnaise or oil—2 teaspoons, Milk—1 cup

Dinner

Lean meat, fish or fowl—1 medium serving ($\frac{1}{4}$ pound raw), Potato—1 small (size of egg), or bread—1 slice, or noodles, rice, corn, or beans— $\frac{1}{2}$ cup, Vegetables—2 generous servings (2 cups), Butter—1 square, Fruit—1 serving

One serving fruit $\frac{1}{2}$ grapefruit, 1 small orange, 1 cup fresh berries, (no loganberries), $\frac{1}{2}$ cantaloupe, $\frac{1}{2}$ slice watermelon (1 $\frac{1}{2}$ inches thick), 3 apricots, 1 small peach, 2 plums, 2 thin slices fresh pineapple, $\frac{1}{2}$ medium apple, 3 nectarines, $\frac{1}{2}$ medium pear, 2 figs, $\frac{1}{2}$ banana, 1 cup grapefruit juice, 1 cup tomato juice, $\frac{1}{2}$ cup orange juice, $\frac{1}{2}$ cup pineapple juice, $\frac{1}{2}$ cup dried cooked apricots or prunes (when stewed without sugar)

May take Clear soup, plain tea or coffee with any meal Saccharin ($\frac{1}{4}$ grain) may be used for sweetening, if desired. Any kind of bread may be used, but only in the amounts specified

Avoid Sweets, such as sweetened canned fruit, honey, sugar, all desserts, and fruits which are not listed here

It is important not to eat larger helpings than those listed here

III Diet 2062 Calories

Carbohydrates 220 Gm, Protein 93 Gm, Fat 90 Gm
Breakfast

Fruit—1 serving, Cereal—3 tablespoons (dry measure before cooking), Milk—1 standard measuring cup (or $\frac{1}{2}$ cup canned milk), Bread—1 slice, Butter—1 pat, Egg—1

Lunch

Meat, fish or cheese or eggs—1 small serving ($\frac{1}{8}$ pound = 2 oz), Vegetables (raw or cooked)—1 generous serving (1 cup), Bread—2 slices, Butter, mayonnaise, or oil—2 pats, or 4 teaspoons, Fruit—1 serving, Milk—1 cup

Dinner

Lean meat, fish or fowl—1 medium serving ($\frac{1}{4}$ pound raw), Potato, or bread—1 medium, or 2 slices, Vegetables (raw or cooked) except corn, beans, peas—1 generous serving (1 cup), Butter, mayonnaise, or oil—2 pats, or 4 teaspoons, Fruit—1 serving

One serving fruit 2 oranges or 1 cup juice, 1 large grapefruit, or 1 cup juice, 1 small cantaloupe, 2 cups fresh berries, 1 slice watermelon (2 inches), 7 apricots, 1 large peach, 1 slice canned (sweetened) pineapple, 1 cup pineapple juice, 6 plums, 1 apple, 1 medium bunch grapes ($\frac{1}{2}$ pound), 6 nectarines, 1 pear, 30 cherries, 4 figs, 1 small persimmon, 1 banana, 5 prunes, or $\frac{1}{2}$ cup stewed dried fruit (cooked without sugar)

Instead of one serving fruit, $\frac{1}{2}$ cup of jello, custard or junket may be used occasionally

Instead of 1 medium potato, the following may be used 1 cup green peas, 2 medium ears fresh corn or $\frac{3}{4}$ cup canned corn, or $\frac{3}{4}$ cup cooked beans, rice noodles or macaroni

May take Clear broth, plain tea or coffee with any meal Saccharin ($\frac{1}{4}$ grain) may be used for sweetening, if desired

Avoid Sweets, such as sweetened canned fruit, honey, sugar, and desserts

Eat all listed for breakfast, lunch and dinner, but only in the amounts prescribed

IV Diet 2550 Calories

Carbohydrate 295 Gm, Protein 95 Gm, Fat 110 Gm
Breakfast

Fruit—1 serving, Cereal—2 tablespoons, or fruit—1 extra serving, Milk—1 standard measuring cup (or $\frac{1}{2}$ cup canned milk), Bread—2 slices, Butter—2 pats, Egg—1

Lunch

Choice of

1 Meat or cheese or egg—1 slice, or 1, Vegetables (except potatoes, corn, peas, beans)—1 cup, Rice or noodles— $\frac{3}{4}$ cup, Bread—2 slices, Butter—2 pats, or oil or mayonnaise— $\frac{3}{4}$ cup

2 Macaroni and cheese or similar creamed dish, or canned beans, lima beans, peas or corn— $\frac{3}{4}$ cup, Vegetables (except as noted above)—1 cup, Bread—2 slices, Butter—2 pats, or oil or mayonnaise—4 teaspoons

3 Meat or cheese or egg—1 slice, or 1, Vegetables, raw or cooked (except as noted above)—1 cup, Bread—4 slices, Butter—2 pats, or oil or mayonnaise—4 teaspoons, Fruit—1 serving, Milk—1 cup

Supper

Lean meat, fish or fowl—1 medium serving ($\frac{1}{4}$ pound raw), Potato—1 medium or bread—2 slices, Vegetables (except as noted above)—1 cup, Butter—1 pat, Salad oil or mayonnaise—1 tablespoon, Milk—1 cup, Fruit—1 small serving or occasionally ice cream pudding or unfrosted cake

Bedtime nourishment

Fruit—1 serving

One serving fruit 2 oranges, or 1 cup juice, 1 large grapefruit, or 1 cup juice, 1 small cantaloupe, 2 cups fresh berries, 1 slice watermelon (2 inches thick), 7 apricots, 1 large peach, 1 slice canned (sweetened) pineapple, or $\frac{1}{2}$ cup canned (sweetened) peach or pear, 1 cup pineapple juice, 6 plums, 1 apple, 1 medium bunch grapes ($\frac{1}{2}$ pound), 6 nectarines, 1 pear, 30 cherries, 1 banana, 5 prunes, or $\frac{1}{2}$ cup cooked (without sugar) dried fruit

Use as desired Clear soup, or plain tea or coffee

Measure all servings Do not overeat. Avoid concentrated foods such as candy, honey, jam, syrup, and sugar

Constipation: Clinical and Roentgenologic Evaluation of the Use of Bran

By

M H STREICHER, M D

and

LUCILLE QUIRK, R N

CHICAGO ILLINOIS

FOR many years bran has been used as a laxative, apparently with some encouraging results and has become generally accepted as a preventive dietary agent in constipation. The literature, however, bears

very little evidence to place this contention on a scientific basis

In 1940, Fantus, Kopstein and Schmidt (1) made a systematic study of intestinal motility as influenced by bran, in this work bran was administered to normal individuals and the intestinal motility was determined by roentgenograms. Two distinct observations were made by Fantus and his co-workers, first,

*From the Departments of Pharmacology and Therapeutics and Medicine University of Illinois College of Medicine Chicago. Assisted by a grant from the Kellogg Company Battle Creek Michigan.
The Roentgenologic work represented in this writing was done by Geza G. Kopstein M D

that bran does not accelerate a twenty-four hour cecal emptying time, but that it does accelerate a forty-eight hour cecal emptying time, and secondly, that the total emptying time of the gastro-intestinal tract is influenced only in the normal individuals who had a forty-eight hour or longer cecal emptying time

The present study is designed to establish the facts about the influence of bran on intestinal evacuation in individuals who are constipated. We selected, therefore, over a considerable period of time a large number of patients with known delayed bowel function and studied the cases clinically and roentgenologically. In the choice of cases for study we were particularly interested in selecting patients who would demonstrate etiologic factors commonly recognized to produce constipation.

The following types were included in this presentation:

1	Habit (irregularities)	54 patients
2	Diet (indiscretion)	35 "
3	Spastic (constipation)	6 "
4	Atonic (constipation)	14 "
5	Mechanical (causes)	26 "

METHOD OF STUDY

Throughout this procedure the patients were not permitted any oral medication or enemas. Each individual was observed at regular intervals before and after routine procedure in our clinic.

At the onset a complete gastro-intestinal study was made roentgenologically by administering 60 to 70 grams of barium sulfate as a water suspension, after complete emptying of the initial barium meal, 30 grams of bran was given to the patient daily for one week, then a gastro-intestinal study made roentgenologically as a second series. While the X-ray studies were made the daily administration of bran was continued. Then the bran was discontinued for one week and the roentgenological study repeated for the third time. In our discussion of the three series of roentgenologic study we refer to cecal emptying time and total emptying time as to results obtained "before," "during," and "after" administration of bran.

RESULTS

A Clinical

In this group we studied a total of 135 patients, fifty-three males and eighty-two females. These were classified into Group I, comprising 53 male patients and Group II of 82 female patients.

For purposes of discussion we subdivided each of the above groups into class A to indicate which patients were clinically improved, class B to show which remained unchanged and class C to indicate which patients became worse after bran intake.

In the following table we tabulate the clinical results obtained in each of the groups described.

TABLE I
Clinical observations made on 135 patients

Groups	No. of Patients Observed	Sex	Clinical Progress by Classes No. of Patients in Each		
			A	B	C
I	53	Male	43	8	2
II	82	Female	64	18	0
Total	135		107	26	2

The results of clinical observations recorded in Table I are subjective findings given to us by the patient. The patients were instructed to record progress made as to daily bowel evacuations before, during and after bran intake and we were obliged to accept their records as authentic. In order therefore to be in a position to evaluate the accuracy of such findings these patients were studied by roentgenograms before, during and after intake of bran so that a correlation was possible.

B Roentgenologic

In recording the findings of roentgenologic studies it is essential to consider the total emptying time and the cecal emptying time of the gastro-intestinal tract.

According to Kopstein (2) a seventy-two hour emptying time of the cecum is considered as delayed motility and a ninety-six hour total emptying time is accepted as a delay in the gastro-intestinal tract.

The results recorded in the Table II show the number of patients studied by roentgenograms which demonstrates delayed cecal and total emptying time while on bran.

TABLE II
Roentgenologic observations made on 135 patients

Group	No. of Patients Observed	Sex	No. of Patients Showing Delayed Motility	
			Cecal Time	Total Time
I	53	Male	7	2
II	82	Female	9	26
Total	135		16	28

Another item that became of interest is the question of improvement in bowel activity with the aid of bran as compared with bowel activity recorded before bran intake and after bran was discontinued. The following table shows the above comparison in 135 patients studied roentgenologically.

TABLE III
Comparative roentgenologic study of 135 patients

Group	No. of Patients Observed	Sex	No. of Patients with Delayed Cecal Emptying Time			No. of Patients with Delayed Total Emptying Time		
			Before	During	After	Before	During	After
I	53	Male	12	7	10	30	27	32
II	82	Female	19	9	14	60	36	52
Total	135		31	16	24	90	63	84

DISCUSSION

It is essential to point out that the patients were studied subjectively and that the clinical findings were further verified by roentgenologic observation. Our problem in general was to determine the effect of the administration of bran orally on bowel activity.

In Table I it is evident that of 135 patients studied 107 were recorded as having improved clinically, 26 remained unchanged in bowel activity and 2 were worse.

In Table II it shows that of the 135 patients studied roentgenologically 16 showed delayed cecal emptying time whereas 63 patients only demonstrated delayed total emptying time of the gastro-intestinal tract.

Another interesting study was to determine the number of patients that were classified as having delayed bowel activity roentgenologically before intake of bran and after bran was discontinued by comparison to the number registered as of delayed activity while on bran. Of the 135 patients studied 31 demonstrated delayed cecal emptying time before bran, 16 showed delayed motility while on bran while 24 demonstrated delayed motility after bran was discontinued. This illustrates the fact that of 31 patients with delayed cecal emptying time, 15 were improved as substantiated roentgenologically while on bran. Again, 90

patients demonstrated as showing delayed total emptying time before bran intake, 63 patients were recorded with delayed motility while on bran, this means that 27 patients were improved as demonstrated roentgenologically in total emptying time of the gastro-intestinal tract. Therefore, of the 107 patients that were reported as improved clinically we may record 42 patients in whom improvement in emptying time could be verified roentgenologically.

CONCLUSIONS

1 Of the 135 patients studied, 107 were improved clinically, 26 remained unchanged and 2 became worse.

2 Of 135 patients studied roentgenologically 31 demonstrated delayed cecal emptying time before bran, 16 showed delayed motility while on bran, showing that 15 were improved while on bran. Of 90 patients showing delayed total emptying time before bran, 63 were recorded with delayed motility while on bran, showing that 27 were improved.

3 Bran administered orally aids bowel activity.

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Fluorescein—An Aid in Gastroscopy

By

H M ROBINSON, M D
BROOKLYN NEW YORK

INTRODUCTION

FLUORESCEIN is a dye which has been used for decades to outline corneal ulcers. A drop applied topically to the surface of the eyeball seems to be adsorbed to the ulcerated area and becomes visible by the greenish fluorescent sheen localized to the area of the ulcer.

An application of this principle should be possible with erosions or ulcerations on skin and mucous membrane surfaces.

In the surgical wards at the Coney Island Hospital we used the dye externally where there was a denuded area. For example, a patient had an amputation of the thigh with a resultant granulating wound. Fluorescein was dropped on the wound. At first the entire area of skin, granulation tissue and epithelialized surface were stained an orange color. The room was darkened and the stained area observed through the gastroscope as though it were viewing a similar wound in the stomach. After a few minutes the stain was concentrated in a small irregular area giving a green fluorescent sheen. The surgeon remarked that the ulcer was actually smaller than it appeared to the naked eye without the fluorescein.

I shall now make reference to the use of fluorescein in peripheral vascular disease. This work has been elaborated by Kurt Lange, at the New York Medical College. He has proved the low toxicity of the drug in

humans even when he used it in large doses such as 15 cc of 5% fluorescein (C F Kirk) intravenously. He has noted no reaction in 500 clinical cases. He states that fluorescein is rapidly excreted in the urine and it is no longer visible in the plasma after five hours have elapsed. In our work topically in the stomach, we have used 10 cc of only 1% fluorescein, which should certainly be non-toxic.

GASTROSCOPIC APPLICATION

Reviewing the background of the drug as outlined above, we felt that it might be useful in outlining ulcers of the gastric mucosa, which might otherwise be overlooked or be indefinite by gastrosopic examination.

TECHNIQUE

The Schindler procedure was unaltered except that 10 cc of the fluorescein was permitted to enter the stomach through the Ewald tube after the gastric contents had been drained. The gastroscope was then inserted and the stomach inspected in the usual manner.

The following cases are representative of twenty-two cases in which this method was used.

CASE REPORTS

Case 1 R M, Age 56, complained of epigastric pain for four months coming on 1-2 hours after eating. X-ray series demonstrated a gastric ulcer on the lesser curvature pars media. Gastroscopy was performed using 10 cc of

1% fluorescein. This showed a small area which was prominent because of a green fluorescent sheen. The margins were irregularly outlined and the base of the ulcer was depressed.

Diagnosis: Gastric ulcer.

Case 2. M. R., operated May 1942, for gastric ulcer—posterior gastro-enterostomy being done. Post-operatively X-ray study revealed a normal functioning stoma. Gastroscopecally there were two small areas which appeared greenish brown and fluorescent. The mucosa near the stoma was quite reddened and the adherent exudate did not stain with the fluorescein. Interpretation was localized gastritis with superficial ulcers—post-operative.

Case 3. H. S., age 50, epigastric pain after meals for twenty years. Occult blood in stools, X-ray series—negative.

Gastroscopecy—On anterior wall in pars media there was an area of cobblestone granulated appearance, orange red in color. Superimposed on this area were two small areas of greenish fluorescence near the lesser curvature.

Interpretation—Hypertrophic gastritis with acute superficial ulcerative gastritis.

Case 4. A. J., age 56, loss of 10 pounds in weight in past 6 months. Constant epigastric pains. X-ray revealed a constant filling defect on the anterior wall near lesser curvature. Diagnosed roentgenologically as a carcinoma of the stomach.

Gastroscopecally—The mucosa of the entire stomach appeared pale in color. The rugal folds were fairly small. The blood vessels were visible through the mucosa. This was interpreted as an atrophic gastritis. The mass visualized was the size of a walnut and reddish granular in appearance. Small scattered areas of fluorescent green represented ulcerations of the surface of the tumor mass.

Diagnosis: 1 carcinoma of the stomach with ulceration of mucosa, 2 atrophic gastritis.

CONCLUSIONS

Fluorescein has been used topically on the mucous membrane of the stomach instilled through the Ewald tube. Gastroscopecy was then done in a series of twenty-two cases.

Four cases with positive findings are reported to demonstrate that fluorescein has been helpful in visualizing superficial ulcers of the stomach. The dye aids in outlining and demonstrating the ulcer giving a more accurate estimate of the diameter of the ulceration.

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The Merits of Sigmoidoscopy Preceding a Barium Enema Study of the Colon

By

MEYER GOLOB, M.D.
NEW YORK, NEW YORK

IT would seem very hazardous to draw any conclusions from a single case report. Speaking for myself alone, however, I have adhered to the procedure indicated in the above title for a goodly number of years in my private practice, and I believe I have derived from it not only a sense of precision in my work but a clear cut diagnostic aid. The case covered by this report is an excellent example, and I therefore have ventured its publication.

A woman, aged sixty-three, already diagnosed as having bleeding internal hemorrhoids, came for examination in July, 1939. The dominant symptoms were a sense of incomplete evacuation of the bowel and a repeated urge to empty several times in the early morning hours. During the few days preceding she had noticed blood on the surface of the feces, occasionally she bled frankly. The entire clinical picture was of a very short duration, and, save for the bowel syndrome, general symptomatology and physical findings were essentially negative. A rectal digital examination was non-informative except for a blood-stained withdrawn finger.

Sigmoidoscopy brought into view a mass, easily traumatized warranting a diagnosis of malignancy.

Barium suspension enema revealed no hesitation in the flow of the opaque medium but canalization was noted at a distance of about four inches from the

recto-sigmoid junction cephaloid. The patient did not, however, expel enema fluid.

Roentgenography (Figs. 1 and 2) did not disclose evidence in concert with the sigmoidoscopic observation, indicating the inadequacy in this case of roentgenography not preceded by sigmoidoscopy.

Dr. Walter Gray Crump, Sr., at the Flower Fifth Avenue Hospital, New York, extirpated the mass and from its location succeeded in performing an end to end anastomosis. Dr. L. C. Reid, pathologist, New York Medical College, reported as follows: "Specimen consists of an irregular mass of whitish tissue 6 x 7 cm in area presenting a markedly convoluted surface having the appearance of large intestine. A portion of this surface is distorted by an irregularly shaped convoluted mass 3½ x 5 cm in extent and approximately 2 cm in depth. A large mass of lipomatous tissue is adherent to the entire structure. Microscopic sections show a very abrupt transition from normal large bowel epithelium to an immature neoplastic glandular structure. These immature glandular loops invade all coats and have the characteristic appearance of an adenocarcinoma (grade 1). There is an extensive inflammatory reaction present. Sections of the small round piece of tissue show it to have a fibromuscular structure. No evidence of malignancy is present. Microscopic sections taken of the omentum tabs are negative for malignancy. Pathological Diag-

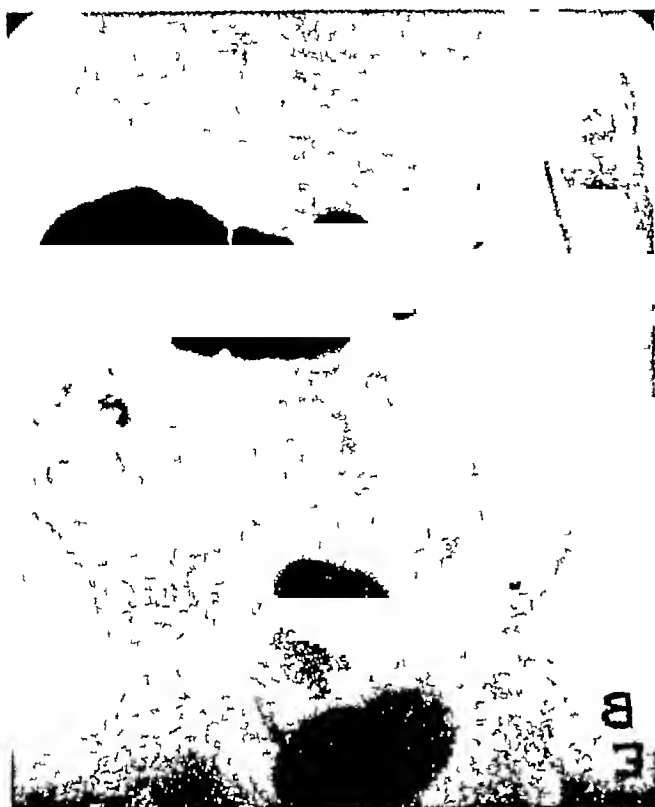


Fig 1

nosis, Sigmoid, Adenocarcinoma (Grade 1)" (Figs 3 and 4)

Under date of September, 1940, Dr. Crump reported the following "There are no hard masses of cancer recurrence in her abdomen. Her liver seems to be



Fig 2

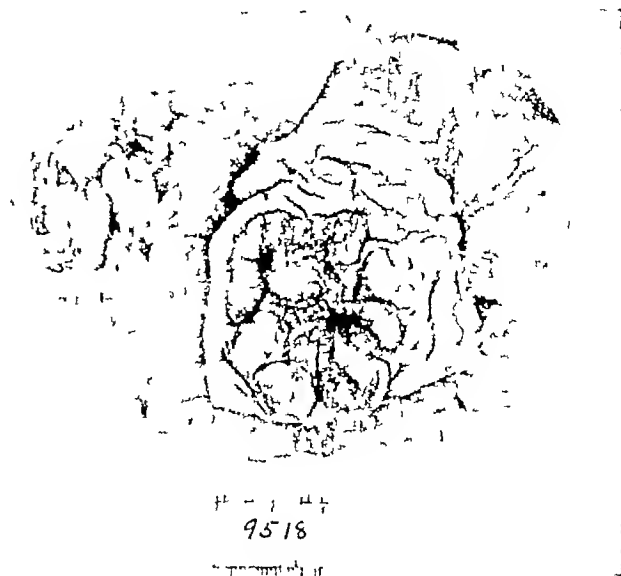


Fig 3

normal and does not project beyond the ribs. The history of her bowel function is excellent." He added, "It is most remarkable that we should have established such results after the removal of so large a segment of bowel involved in cancerous growth—if our results could always be as good as this surgery would be a joy."

That this woman is practically free from symptoms is thus far a most gratifying result, and as far as physical examination is concerned, I find no evidence of recurrence." Nor is there any sign of recurrence at the date of writing, December, 1942. Clinically, the patient is in excellent condition.

DISCUSSION

At the outset, a patient whose symptomatology calls for a colonic study must present himself with the intestinal canal prepared so that the tract is free from stasis—a procedure required for both sigmoidoscopy and roentgenologic study. Time and effort on the part of both patient and doctor are thereby economized to advantage. In the study of colonic pathology, most dependence is ordinarily placed upon a post-evacuation X-ray film. Had sole reliance been placed on this procedure in this particular case, the essentially negative X-ray findings, unfortunately supported by vague symptoms, would have led to a wrong negative diag-



Fig 4

nosis and the delay of radical intervention. To recall Dick's classification of colon carcinomas from the standpoint of prognosis, there are those without nodal involvement and serosal extension, those with nodal extension, those with nodal involvement and serosal extension. The first, of course, offer most favorable prognosis. A timely diagnosis means resectability and no involvement of the regional or distant lymph nodes, timely diagnosis pointedly means timely eradication. If, in addition to timely detection, there is the further advantage that the neoplasm is grade 1, of slow evolution, with no, or very recent metastasis, as in the case under consideration, post-operative longevity is the gratifying result. I am not unmindful of the fact that in proximal colon carcinomas, sigmoidoscopy will be

non-informative, and sole reliance must be placed on the barium enema study. A case was recently referred to me with instructions to do a sigmoidoscopy only and the findings were negative. A roentgenologic study disclosed a naphkin ring defect, luckily without regional or remote metastatic involvement.

CONCLUSION

The two procedures under discussion cannot be dissociated. Either they confirm each other or, when one yields no evidence, the lesion is detected by the other. Through a combination of both procedures the chances of avoiding a wrong negative diagnosis are materially enhanced, and in the presence of a lesion the clinician obtains a well supported affirmative diagnosis.

Allergy as a Factor in Thrombosis

By

JOHN A. TURNBULL, M.D.
BOSTON, MASSACHUSETTS

THE phenomena which we have agreed to designate as 'allergic,' appear to have a common origin, no matter how widely different their manner of manifestation. This origin would seem to be certain disturbances in the physical and colloidal-chemical mechanisms of the blood and other body tissues. The evidence in substantiation of these assumptions is the identity of the blood and tissue changes in different species of animals used in experimentation, and in different human beings whose outward manifestations may be as widely variant in nature as are gastro-intestinal allergy and—let us say—angioneurotic edema.

Though we have learned much about allergy in the past two decades our knowledge has not yet reached a point where we can offer ourselves an exact explanation of the physio-chemical disturbances which we have learned to recognize. The most reasonable hypothesis is that such disturbances are the manifestation of stimulation and depression of cellular activity. Such cellular disturbances constitute an alteration in normal function which we recognize as a "crisis," reaction, or symptom-complex related to definite causal factors. (1) The important step is to recognize the underlying similarity of these different manifestations. We must disregard superficial differences in looking for this basic similarity.

The idea that femoral thrombosis might be an allergic manifestation was suggested to me by the history of several patients who consulted me for other physical disabilities. In each case thrombosis loomed large in the clinical picture, although it was not regarded as the chief factor in the patient's ill health. The success which attended treatment applied in accordance with this view is the occasion for this paper.

Consultation of such authorities on medical practice as Osler's *Modern Medicine* or Delafield and Prudden's *Text-book of Pathology*, or the *System of Medicine* edited by Sir Clifford Allbutt informs us that Thrombosis is the formation of a clot or solid coagulum in the blood vessels or heart of the living animal, the

coagulation or agglutination of the formed elements of the blood into a more or less coherent mass during life.

The formation of a thrombus is usually the result of a traumatic injury to a blood vessel, it may follow compression or dilatation of such a blood vessel. Again invasion of the blood vessel by infection or some other disease agent may result in thrombosis of that vessel, and any factor bringing about retardation of the rate of circulation of the blood may act in like manner. So long as the endothelial lining of the vessels is intact simple retardation of the circulation alone probably would not result in the formation of a thrombus. Coagulation will, however, be favored by any pathologic changes in the endothelium, such as inflammation, degeneration, calcification, or the mere presence of bacteria in the circulating blood. The entrance of bacterial toxins in the blood stream, such as occurs in puerperal infection or the secondary infection of malignant growths, offers peculiarly favorable conditions for thrombosis. (2) Thus, it takes place not infrequently in the course of infectious diseases and may also complicate the conditions of malnutrition and general cachexia seen in many acute and chronic systemic diseases.

Nearly a quarter century ago, Ludwig Aschoff (3) delivering the Cartwright Lecture before Columbia University's College of Physicians and Surgeons, enumerated the chief causes of thrombus formation as follows: (1) Changes in the blood plasma (diminished or increased coagulability), (2) Changes in the blood elements (increased or diminished powers of agglutination), (3) Changes in the blood flow (slowing and formation of eddies), and (4) Changes in the vessel wall itself (endothelial damage).

Although it is generally admitted that fibrin coagulation must in some way be increased, in order to permit thrombi to form, the existence of increased coagulability is not according to Aschoff, the first stage of thrombosis. Important changes in the morphological constituents of the blood must precede it. As the result of an extended series of animal experi-

ments he concluded that the slowing of the blood stream and the alteration of the blood elements themselves, especially alterations of the blood platelets, are the chief factors in the production, not only of the static, but of toxic thrombosis as well. In static thrombosis retardation of the rate of circulatory flow is of prime importance, for the toxic varieties, changes in the blood elements have the dominating influence.

This concerns the first phase of the thrombotic process. Coagulation of fibrin seems inevitably to follow thrombosis from any cause. But the first stage is the erection of a morphological structure by a process of *agglutination*. Fibrin ferment can then be provided by the elements which have agglutinated. Coagulation of these elements is thus promoted, and the *second phase* of the thrombotic process is accomplished.

The part played by infection in the origin and establishment of thrombi is minimized by Aschoff. Later writers are still divided on this question. "In the case of distant thrombosis the infection usually arises in already existing thrombi and cannot be regarded as the source of the thrombosis but rather as an accompanying or induced phenomenon." After operative procedure, or in already established infection thrombosis at a distance is of frequent occurrence. It is well known that in acutely progressing septic cases, thrombosis at a distance is much rarer than in sub-acute or chronic cases. That in itself speaks against a direct action of infection."

After extensive animal experimentation and checking of the findings of others, Rosenthal (4) concluded that stasis and endothelial injury do not lead to thrombosis, although both may play important roles. *Blood changes are prerequisite* (italics mine). But when he comes to discuss the nature of the changes, Rosenthal does not speak so positively. Reviewing the literature, he tells us:

Dietrich (5) championed the importance of infection in thrombosis. He agreed with Klemensiewicz that a thin layer of a homogeneous substance forms on the endothelium at the site of the thrombus. This, he explained, is the result of a sensitization of the endothelium, after which there is a direct reaction between endothelium and blood to form the thrombus. All these factors are directly influenced by chronic infections, stasis merely acts in localizing the clot. Experimentally sensitization of an organism has resulted in foci of endothelial proliferation. Actual thrombosis has been produced when suppuration was introduced with stasis (Dietrich and Schroeder, Miller and Rogers). Juegens, by the use of a capillary thrombometer, found an increase in clotting time in infections.

Pfleiderer (6) discussing the increase of embolism and thrombosis in post-war Germany, hazards the opinion that sensitization to various articles of food to alcohol or to tobacco, may be a predisposing factor in the production of these lesions of the blood vessels. He regards this as of more etiologic importance than infection. During the past year two writers in the German language have added data in regard to the part played by sensitization in the formation of thrombi. The Russian obstetricians, Szerdjukoff and Jegoroff (7), reported upon an autopsy performed on the body of a woman who had died of malignant metastasis two years after panhysterectomy, followed

by extensive Roentgen irradiation, the original lesion being cancer of the uterine cervix. The immediate cause of death, however, was thrombosis of the left iliac and femoral veins. Necropsy, much to the authors' surprise, showed no cancer cells in the veins, nor in the thrombotic masses which occluded them. The theory is advanced that the decomposing products of the original cancer, which were rendered more toxic because of the additional treatment by Roentgen-rays, had entered the circulation and so sensitized the intima of the blood vessels as to cause formation of thrombi. The condition therefore, might be regarded as an allergic reaction.

The results of the animal experimentation carried on by Knepper and Waaler (8) at the pathological laboratories in Oslo, Sweden, likewise tended to confirm the theory that sensitization may be responsible for thrombosis. By intravenous injection of certain antigens they produced in the large blood vessels of their subjects a condition which they term "hyperergische arteritis," that is inflammation of the intima of the arteries because of the presence within these vessels of an excessive amount of the *cign*—the substance supposed to be present in the body fluids which, by uniting with the *allergen* of the infecting material, produces allergy. In their first experiments the Swedish investigators used from 20 to 30 ccm of the selected antigen. Later they found that when the experimental animals were made to exert themselves, thus putting an increased burden upon the heart, a much smaller quantity of antigen sufficed to induce the condition in the arteries—1 to 2 ccm, being enough to affect the chief organs of the vascular system—lungs and heart.

Though these results may seem rather meagre evidence for confirmation of the theory that allergy may play a deciding role in the production of thrombosis, it is certainly highly *suggestive*, even if it cannot be termed *conclusive*. In any event the subject would seem to be of sufficient importance to warrant the publication of the following case reports. It is to be hoped that others who have had similar experiences in clinical work, will be encouraged to report what they have seen and the conclusions which have been drawn therefrom.

CASE REPORTS

Case 1. In July, 1914, I was able to institute an Anaphylactic Clinic at the Massachusetts General Hospital, which I conducted for the succeeding five years. In the course of my work there, while making a cutaneous test upon a patient's forearm, just below the antecubital space, I noted within three minutes, a local reaction of reddening at the site of scarification. In five minutes more this redness had extended along the median cephalic and median basilic veins, while a wheal formed at the original site. A brightening redness traversed the course of the cephalic vein as far as the acromion process, while on the track of the basilic, on either side the biceps, the coloration reached the point where this vein pierces the deep fascia just below the middle of the arm. The redness in wheal and along the veins reached a maximum of brightness in about eighteen minutes, maintained this tint for about eight minutes, and then gradually faded. In 20 minutes the color had entirely disappeared and the patient suffered no greater inconvenience than some itching at the site of scarification.

I several times tested this same patient in this way, to demonstrate this peculiar reaction, always being able to obtain it when I selected the same site for introducing

the test material. To me this unusual reaction—among thousands of sensitization tests made annually under practically identical conditions—indicates that substances to which an individual is sensitive may induce inflammation in the vascular system if the conditions are favorable. In this particular patient it is possible that only the walls of the veins, and not the endothelium, were affected by the sensitizing protein. Or, if the endothelium was affected, there was not a sufficient disturbance of the venous endothelium, or a sufficient length of time to induce those blood changes which would have brought about thrombosis. Had it been possible to repeat this experiment at short intervals, so that the inflammatory condition would have been kept up, blood changes enough to induce thrombosis would probably have occurred.

Writing in Christopher's recently published *Text-book of Surgery by American Authors*, de Takets (9) would seem to hold a similar view, when he states:

In addition (to trauma) one must consider an increased reactivity of the vascular endothelium to injuries of bacterial or toxic nature. Thus it has been possible to sensitize the vascular endothelium experimentally with bacterial protein or split products of protein. Such an intima is in a state of vulnerability and responds with fibrinous exudate at the slightest provocation, thus giving the initial impetus for thrombosis. The conception of such a vascular allergy explains many of the hitherto unexplainable findings in spontaneous and post-operative thrombosis, or migrating phlebitis.

Case 2. On January 20, 1920, a married woman of 63 years consulted me for precordial pain. For the previous two years she had suffered frequent attacks when the knife-sharp pain radiated to the left shoulder and down the arm to the finger-tips. These occurred nearly every day, between 2 and 4 in the morning, or at any time on the slightest extra exertion or excitement. She at once gave me an exposition of these symptoms, for the mere excitement of coming into the presence of a stranger, produced a typical attack during which she could only gasp, with her hand over the precordial area, "I can't talk, I'm having an attack of just what I came to see you for."

In taking the history (when the attack had passed) she informed me that there was always the passage of much flatus during the attacks, although they did not seem to bear any relation to eating. I found the right leg slightly larger than the left, with skin and subcutaneous tissue thick and indurated. The skin of the leg had a mottled appearance, while numerous varicose veins were in evidence on the lower third of the thigh, extending down to the knee. She complained of continuous pain on the inner side of this leg, usually worse at night so that massage was necessary before she could go to sleep. The leg condition had originated after childbirth in 1885 (35 years previously) but had been much worse since the onset of the precordial attacks two years before. The right femoral vein proved very sensitive to palpation, giving a feel as of a hard cord for its entire length.

The family history was suggestive only in the finding that a sister had suffered from arthritis. The patient herself had as a child been subject to "sick headaches." After I had made the tests to ascertain the foods to which she was sensitive, a diet was outlined in accordance with the test findings. The patient was very skeptical as to the possibility of a mere diet relieving her of the precordial pain, or lessening the almost lifelong difficulty with the right leg. When she had been persuaded to try it for two weeks, she remarked, "If I think it is doing me any good, I'll telephone you for an appointment."

The appointed fortnight ended after five days of severe snowstorm. The patient arrived at the office after a strenuous journey in a taxicab, through streets still blocked with snow. She had had "excitement a-plenty"

being tumbled about the taxi in all directions, but she had suffered no precordial attack. She had not had one since beginning the diet. The right leg had almost ceased to pain, only slight rubbing gave complete relief, the soreness, and swelling had entirely disappeared. On examination the varicose veins could not be seen.

She remained well until June 20, just five months after the institution of the dietary restrictions. On that day her husband persuaded her to eat some salmon—one of the foods to which she gave an allergic reaction. Within five hours there was severe precordial distress, accumulation of flatus, swelling of the right leg, and return of the tender, cord-like swelling of the veins. These symptoms reached their apex in 24 hours, then gradually receded, so that after five days of strict adherence to the diet, she was free from pain, and all evidence of venous inflammation had subsided.

It is probable that the same changes which were outwardly visible in the femoral vein took place in the coronary arteries, although the inflammation was not severe enough to cause complete occlusion.

Case 3. A married woman, aged 33 years, had suffered from abnormal frequency of bowel evacuation for more than eight months previous to consulting me on July 5, 1933. The attacks appeared to come in cycles although she never had less than four evacuations a day. The cycles appeared to be six days in length, the number of movements on the sixth day being often as high as twelve, accompanied by severe cramps. At the peak the feces would be black in color, the tint gradually lightening as the attack receded, until a few days preceding the onset of another attack the color would be a light yellow. Gas was present all the time, increasing as the attack became more severe. Three days before the onset there was always a "bad taste" in the mouth, and later abdominal pain (worse in the lower left quadrant), cold extremities and general chilliness, general physical malaise and great mental depression. She had had eczema as a child, urticaria from the age of fourteen, and headache at the end of the menstrual period the onset of which had been at the age of 15 years. The flow started regularly on the 28th day but after a two-day normal flow, would "dribble" for a short time, and then "spurt" about the fourth and seventh days.

Examination showed eczema still in evidence on the chest, low down to the right of the sternum, both sacroiliac joints were arthritic, while the right femoral vein displayed a cord-like hardness and great tenderness on manipulation. The femoral varicosity had persisted since childbirth twelve years before, and the pain and soreness were said to be worse preceding a storm and at night especially if walking were indulged in during the preceding day. The laboratory reports were:

BLOOD			
Hæmoglobin	85	Fasting blood sugar	93
Red cells	4,650,000	Blood uric acid	2.84
White cells	6575	Blood sugar tolerance (14 hrs after administration of 100 gr Dextrose)	57
Polymorphs	75		
Large lymphocyt.	3		
Small lymphocyt.	21		
Endothelial cells	1		
BASAL METABOLISM	9	WASSERMAN —Negative	
URINE			
Clear, normal color		Sediment	
Sp. gr. 1.002		Few squamous cells	
No sugar		Few round cells	
No albumen		Rare leukocyte	
BLOOD PRESSURE	Systolic—95	diastolic—60	
PULSE RATE —110			

A diet was prescribed in accordance with the results obtained from cutaneous testing. Turnbull Diet No. 9 has proved most effective in arthritis (9). No other treatment. In two weeks there was complete relief from the bowel disturbance, the arthritis had disappeared, and the cord-

like hardness and tenderness in the femoral vein was completely relieved. Bowel movements were reduced to two or three per day at the maximum, and the other symptoms subsided permanently.

In this case there was a definite history of allergy in the childhood eczema and urticaria. Increased sensitization in adult life led to the intestinal tract and venous allergy at a later period. Although femoral thrombosis following childbirth is occasionally seen, it is a rare condition, and doubtless, there is always a predisposing cause for its occurrence at this time. In the allergic condition of this patient, long previous to pregnancy, we can trace the factor which caused changes in the blood stream and the veins themselves. Inflammation of the endothelium, with blood coagulation, and later agglutination of the formed elements is a logical sequence, and explains the arthritis, the pain and soreness in the femoral vein and the other distressing symptoms, as well as the intestinal allergy which produced the frequent bowel movements.

Case 4. Excruciating pain in her right leg brought to me in consultation, a married woman of 56 years, whom I first saw on February 24, 1930. The condition had first been in evidence in 1900, when the patient was 26 years of age. Pain and soreness on the inner right thigh had increased in intensity for five years. Thereafter the condition had remained stationary, but the pain and sensation of weight in the right leg had always made walking difficult if not impossible. Consequently, she had remained in bed much of the time, as she was only comfortable when she could maintain the leg out of the dependent position. A severe uterine hemorrhage ten years before (1920) had necessitated hysterectomy for fibroids. There had been no pregnancies, and no history of allergy could be recalled by the patient. She had been "tired all the time." Amputation of the affected leg had been advised by a well known surgeon when she was 31 years of age.

BLOOD EXAMINATION				BLOOD EXAMINATION			
Hemoglobin	80	White cells		Uric acid			4 mg
Lymphocytes	25		5600	Fasting blood sugar			105 mg
Polymorphs.	66	Red cells		Sugar (1½ hrs after 100			
Transitionals	2		5 010 000	gm Dextrose)			137 mg
Mononuclears	6						
Mast cells	1						
Renal metabolism	3			WASSERMANN—Negative			
BLOOD PRESSURE		Systolic—122		diastolic—75			
URINE							
Fasting urine				Urine 1½ hrs after Dextrose 100			
Pale clear acid Sp gr		1 020	µm	Pale clear acid Sp gr		1 020	
Albumen slight trace				Albumen slight trace			
Sugar none				Sugar none			
Sediment Few red cells little mucus few hyaline and granular casts							

Examination of the leg showed it to be greatly swollen, the patient complaining that the pain radiated from the groin, along the inner aspect of the thigh, back of the knee as far as the toes, the entire leg "feeling as if it would burst." The skin was white and glistening, some areas showing papillation.

Detecting in this case an analogy of Cases 1 and 2, I decided to place this patient upon a diet, as indicated by cutaneous testing, despite the absence of any direct history of allergy. As the patient complained that the pain extended into the sacro-iliac and lumbar regions it seemed probable that there was a continuation of a thrombosis of the popliteal and femoral arteries into the external iliac and internal iliac veins. Some idea of the amount of swelling may be gained by comparison of the measurements of the right and left legs at the beginning of treatment by diet.

Within two weeks of the time this patient was placed upon a diet, the ingredients of which were determined by careful cutaneous testing, there was a marked reduction in the tenderness and hard cord-like feeling in the popliteal

and femoral veins, the tension and induration of the skin of the leg, and in the pain and soreness throughout that area. The papillary condition disappeared and the pain previously experienced in the sacro-iliac and lumbar regions was almost completely relieved. Improvement continued until at present this woman takes a new interest in life, is no longer "always tired", the leg itself has lost its sensation of leaden weight, so that she can once more enter upon the usual social activities of her position in life. The blood pressure is now *systolic*, 128, *diastolic*, 75. So long as she adheres strictly to the prescribed diet this patient remains practically free from her former symptoms, but no sooner does she eat any forbidden foods than the leg begins to pain, and soreness along the popliteal and femoral veins is once more in evidence. At the beginning of 1933 she developed head colds and sore throat, and on

	Right Leg	Left Leg
At level of inferior border symphysis pubis	26 inches	18¾ inches
Six inches above upper border of patella (leg fully extended)	25½	17¾
Upper edge of patella (leg extended)	21½	13¾
Seven inches below lower border of patella (leg extended)	17½	10¾
At tip of external and internal malleolus	11½	8¾

close questioning admitted that she had been taking milk, which was on the prohibited list. Omitting the milk from her diet did away with these respiratory reactions, and she has since remained well. After 3 months on the diet there was a reduction in the measurements of the right leg averaging more than two inches throughout, and this improvement has been steadily maintained, although the right leg remains perceptibly larger than the left.

COMMENT

These four cases, taken in connection with reports previously made in literature, strongly suggest an etiological relationship between allergy and thrombosis. It is noteworthy that only one patient came under my attention because of thrombosis primarily. The condition presented by the patient in Case 4 might properly be termed 'elephantiasis,' which is defined by Warthin as "Those affections of the skin and subcutaneous tissues, characterized by a hyperplasia of the connective tissue, either diffuse or localized to the blood vessels, lymph vessels, or nerves. The most common variety, however, is that one involving the lymphatics." This woman's condition suggests that the relatively rare instances of elephantiasis wherein the blood vessels are affected, may originate in an allergic tendency on the part of the individual manifesting the reaction.

In these three patients aside from the evidences of thrombosis there was a different accompanying condition in each—angina pectoris in Case 2, periodic diarrhea in Case 3, and unilateral hypertrophy of the leg in Case 4. The relationship between these allied conditions, and the sensitization of the intima of the blood vessels common to all three women, is easily recognized. The prompt relief of symptoms, on the elimination of sensitizing foods from the daily ration, is exceedingly striking.

The agreement of the conclusions which I have drawn from these few cases, and the generalization of de Takéts and others, which have recently received considerable publicity, should stimulate more extended research along the lines indicated

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Meckel's Diverticulum Containing Calculi

Case Report

By

F. W. MULSOW, M.D., Ph.D.
CEDAR RAPIDS IOWA

AMONG the acute abdominal conditions which present diagnostic difficulties, diseases of the Meckel's diverticulum are usually considered. In a review of the literature only 9 previous case reports of calculi in a Meckel's diverticulum were found. In the early reports these stones were thought to be gall stones because of their appearance.

Among the early case reports is one described by Beach (1) which occurred in a woman 62 years old. The stone was the size of a pigeon egg, and was found in a sac lined with intestinal mucosa connected to the lower ileum and adherent to the urinary bladder.

Sherren (2) reports the case of a man 38 years old, who had symptoms of recurrent appendicitis and about 6 months later passed with the feces what appeared to be gall stones. A few months later at an abdominal operation, the gall bladder was found to appear normal but a Meckel's diverticulum was found filled with many small blackish stones. These stones were found to contain cholesterol, calcium oxalate, and bile pigments. Sherren refers to 4 previous reports, but in only one of these was I able to read the original report, the one reported by Znojensky (3), who operated upon a boy 18 years old and found a Meckel's diverticulum containing what he called a gall stone incarcerated in the outer retrocecal recess. The other cases referred to were the one by Beal (4) who at an autopsy of a boy that had died of peritonitis from a perforated Meckel's diverticulum, in which he found a cherry stone, the coriaceous covering of several orange pits and 2 masses of irregular form resembling concretions found in the intestine of horses. The two other case reports to which Sherren referred were by Galeazzi (5), who found an apparent gall stone in the purulent contents of a Meckel's diverticulum and Hollander (5), who operated upon a man for apparent acute appendicitis but found instead a gangrenous Meckel's diverticulum filled with what he considered to be gall stones, and which were faceted and contained cholesterol.

Drummond (6) reports the case of a 27 year-old man, who at the operation was found to have a small stone weighing 12 grains, which had perforated the Meckel's diverticulum and was free in the abdominal

cavity. This stone was found to contain fecal material and bile pigments.

Hanke (7) reports the case of a 69 year-old man who died of cardiac failure and hypertension and at the autopsy he found also chronic cholecystitis and cholelithiasis and a Meckel's diverticulum which contained 15 apparent gall stones. About half of these were faceted and the size of a pea and the rest were smaller and faceted. These stones were later examined chemically and with the spectroscope by Gerlach (8), who found that they contained considerable amounts of zinc and small amounts of lead, copper, iron, manganese and silicon. He found the composition of gall stones quite different.

Hagler and Stewart (9) in discussing the foreign bodies that had been found in the Meckel's diverticulum, make no mention of stones being found in it, but mention coproliths, apple seeds, cherry stones, a needle, a Murphy button, fish bone, and pieces of orange peel.

Quenu (10) reports a case of a Meckel's diverticulum which was found in an inguinal hernia and which contained a calculus.

CASE REPORT

This man, Mr. F. E., a 48 year-old farmer, while at work in the field about 11 a.m., was seized with sudden, severe, cramping epigastric pain. He felt faint and began to sweat profusely. He had no nausea or vomiting, although his bowels had moved apparently normal twice during the morning and forenoon. He gave a history of having had 3 similar attacks which quickly subsided.

On arrival at the hospital the temperature was 98°, the pulse 60, respirations 20, and the blood pressure 130/90. He complained of severe pain and deep tenderness in the epigastrium. There were no abdominal masses or rigidity. The heart was not enlarged to percussion. The heart sounds were faint and no murmurs could be heard. The urine was slightly alkaline and showed a trace of albumen. The white blood count was 11,300.

With so little definite abdominal findings, absence of fever, and low white count, a consultant was called. The medical consultant considered the possibility of coronary occlusion because of an inverted T, in the electrocardiogram and the other physical findings. Morphine was given for the pain and for rest. The next morning the white

blood count was 16,000. There was now diffuse abdominal pain and muscle rigidity, and a diagnosis of an acute abdominal condition was made.

About 22 hours after entering the hospital, the surgeon, Dr C B Meffert, found at the operation a small amount of free fluid in the abdomen and a bluish nodular mass, resembling a kidney, slightly to the right of the mid-epigastrium. On further exposure this was found to be a large gangrenous Meckel's diverticulum impacted with

extensive gangrene of the mucosa which had the appearance of intestinal mucosa.

The pathological diagnosis was gangrenous Meckel's diverticulum with calculi impacted in its proximal lumen, and acute appendicitis with a concretion in its lumen.

DISCUSSION

Reports of calculi in Meckel's diverticulum are very rare. Only 9 previous reports of this condition could be found, yet it has been estimated by various authors that 1 to 2 per cent of people have a Meckel's diverticulum. There are many reports in the literature of diseases of it, yet only 2 case reports of calculi in it could be found in the American literature. Such calculi when seen in X-ray examinations might be mistaken for calcified lymph nodes, renal calculi or phleboliths. These stones have the appearance of gall stones and have been mistaken for gall stones in a few instances. It appears, however, that by proper physical and chemical examinations they can be distinguished from gall stones. In the present case the stones were obviously formed in the diverticulum. The association of an acute appendix with the acute diverticulitis or other acute abdominal conditions is not unexpected, and in the present instance reveals the value of a thorough exploration where possible in acute abdomi-



Fig 1 Meckel's diverticulum with stones in it

stones. Because of its thick wall it was difficult to remove. The appendix was also acutely inflamed and posterior and medial to the cecum. It was closely adherent to the posterior peritoneum.

PATHOLOGICAL REPORT

The Meckel's diverticulum is 9 by 6 by 4 cm. It is blackish red and has a foul odor. The wall is 5 to 12 mm thick and contains considerable fatty tissue. Its cavity is filled with 5 large faceted brownish stones and a small amount of bloody purulent fluid. The largest stone is 3.5 cm across by 2.5 cm thick and is impacted into the mouth of the diverticulum. The other stones are flat, and slightly elliptical. The largest one is 3 by 2.3 by 1 cm and the smallest is 2.4 by 1.8 by 7 mm. One stone was broken and found to be formed in layers and contained fecal material, bile pigments, and calcium carbonate. Another stone was given to the patient and the diverticulum with the remaining stones are shown in the photograph. X-ray examinations of the stones show them to be formed in layers and to contain material that is opaque to the X-ray.

Microscopic sections showed the wall to contain considerable fat and scar tissue, with many leucocytes and red cells scattered through the sections. There was



Fig 2 Meckel's diverticulum and its stones

nal conditions. The patient made an uneventful recovery and has had no further trouble.

CONCLUSIONS

A case is reported in which calculi were formed and became impacted in a Meckel's diverticulum. Such calculi have been mistaken for gall stones and in a like manner might be visible upon X-ray examinations.

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The Normal Appearing Gall Bladder (Report of 32 Operated Cases, With Long Follow Up)

By

J RUSSELL VERBRYCKE, JR., M D *
WASHINGTON, D C

TO operate for cholecystitis, after careful study of the patient, only to be confronted by a bluish organ of soft consistency and even perhaps without adhesions, is one of life's most embarrassing moments to the conscientious surgeon. Hopefully, and also woefully, he examines everything else in the abdomen to find another cause for the abdominal symptoms, removing the appendix, if it has been left for him. With nothing else found the operator goes desperately back to the gall bladder for a final decision. There may be a lack of lustre, a bit of yellowish discoloration in places but again it may appear blue and normal to sight and touch. Should it be removed, or not?

To remove an organ, even one with the relatively unimportant functions of the gall bladder, does not appeal to one as being a good thing to do if there be no disease. On the other hand, it is even worse to close the abdomen, without accomplishment, only to have the patient complain of the same symptoms which originally prompted the operation.

Cattell feels that a gall bladder should be removed when there is a history suggesting cholelithic disease, when theograms are suspicious or show pathology and where other gastro-intestinal disease is ruled out. He says, "If sufficient evidence existed to cause operation, it should be removed in the absence of other pathology to account for symptoms."

Graham once said in a discussion, "I would rather trust the results of cholecystography than my senses of sight and touch at operation," and proceeded to show several specimens of marked strawberry disease with the serosal surface entirely normal.

I thoroughly agree with both of these pronouncements. After seeing some gall bladders left in with a continuance of symptoms and after removing several which in spite of typical symptomatology, and non-visualization, appeared quite normal and after finding mucosal disease or even small stones which could not be felt before removal and finally after seeing relief of the symptoms, I now have no compunction when confronted with these circumstances and when no other pathology can be found.

From a fairly large gall bladder series I have collected 32 such cases of comparatively normal appearing gall bladders which I have removed. Some were not normal in that adhesions were present. In others there was hepatitis but in none was there much gross pathology of the organ itself evidenced by sight or feel at the operation.

It is thought to be of interest to present these cases and their outcome particularly in view of the rather poor end results which have been reported following operation on the non-calculous gall bladder which may have been even more grossly diseased than those

chosen for this series. All were carefully studied before operation from a general and gastro-intestinal stand-point. Some were operated upon before the days of cholecystography but the rest were x-rayed.

SYMPTOMATOLOGY

Upon analysis we find the symptoms and signs of the cases in this series to be not very different from those in any series of chronic cholecystitis, with or without stones. There were 29 women and 3 men, of the usual ages for gall bladder conditions.

Fourteen (43%) had colicky pains, to real colic. Thirteen (40%) had pain of aching or dull character, two (6%) a distress or full discomfort only, and three (9%) only complained of "indigestion" with gas and soreness.

Seven either gave a history in the past, or at the time of examination had one or more acute attacks with fever and leucocytosis. These were the cases which most amazed me by the paucity of pathologic evidence at operation. Obviously however the cause was removed since none of the seven had any subsequent attack.

The usual variety of other abdominal symptoms such as gas, qualitative dyspepsia, etc., was present in this series as will be noted in the case histories.

Localized tenderness over the gall bladder was found at the time of study in 22 or about 68%. In nearly all it became more marked in the upright position and in some was only elicited in this way. Localized muscle stiffness accompanied the tenderness in 9.

CHOLECYSTOGRAMS

Films were made in 22 of the series. Only three gave normal function. In 7 there was no visualization while 11 were called "pathologic without stones" and one "pathologic with stone." Apparently function was interfered with to about as great a degree as in more grossly diseased gall bladder.

OPERATIVE FINDINGS

As has already been mentioned the serous surface of all of these gall bladders was reasonably normal in appearance nor was there much thickening so that the other findings are particularly interesting.

Stones. In 8 cases stones were present including small, soft early stones, small imbedded hard stones which could not be palpated and were not discovered until the gall bladder was opened after removal. Two others showed thick, sticky black bile but no stones.

Strawberry gall bladder. Seven of this series were typical examples of cholesterosis. While grossly diseased strawberry gall bladders do occur still it has always impressed me that this type of lesion is very apt to have thin walls and a normal colored serosa.

*Consultant (Gastro-Intestinal Surgery) to Garfield Memorial Hospital, Washington, D C

So also in this type symptoms are apt to be unusually severe and out of all proportion to the apparent pathology

Case 30 is an excellent example of how normal even an acute strawberry gall bladder can appear. One would hesitate about even admitting the diagnosis if it were not for complete cure and non-recurrence of attacks

Adhesions In 3 cases there were definite adhesions confined to the area of the cystic duct and in one the duct was markedly dilated

Nine gall bladders were adherent to the omentum, duodenum or colon. It is difficult to reconcile this finding with the absence of inflammatory appearance of the serosa if the adhesions are the result of infection and not congenital in character. One is prone to use the presence of adhesions as evidence in proof of present or previous disease but I know of no certain way of differentiating between the acquired and congenital varieties. I have previously described a special syndrome caused by traction on the gall bladder by an adherent hepatic flexure

Hepatitis Another frequent finding which helped to confirm the diagnosis of gall bladder disease in these cases was hepatitis. Acute or subacute hepatitis was noted in seven. Such a designation was made solely upon the gross appearance of a boggy, rounded liver edge, usually of a lighter or rather a brighter color than the normal liver. Chronic hepatitis was noted by white fibrous streaks either localized in the gall bladder region or rather generally through the liver. This condition was present in 5 more cases making a total of 12 out of the 32 who showed liver change

Appendix In 18 patients the appendix was removed as well as the gall bladder. Most operators will agree that the determination as to whether or not a chronic appendix is the likely cause of the symptoms in an individual is more of a problem than the appraisal of the gall bladder. One appendix was definitely congested presenting actual subacute inflammation. Six were adherent, constricted or kinked, 6 were atrophic, 2 presented rather definite chronic disease and 3 others contained fecaliths

Other pathology present Various other pathologic conditions were found including pancreatitis, ileal band, adhesions of duodenum to the lower surface of the liver, ovarian cyst and 2 uterine fibroids. In the main, however, it was felt that the symptoms were caused by the gall bladder and not by the concomitant pathology

RESULTS

No one will be any more surprised to learn of the outcome of the patients in this series than I was myself when I gathered them together and analyzed them. It is usually stated that, in general, the greater the pathology the better will be the result of its correction. One would expect therefore in cases such as these, presenting a more or less normal appearance of the gall bladder, that fully half of the patients would have been unrelieved. But the facts are quite the contrary. Sixteen were 100% cured. Twelve more obtained such good results from the operation that they were eminently pleased. This totals 28 out of 32 or 87.5% in which the result was highly satisfactory. All who are familiar with gall bladder statistics will agree that this is a highly gratifying figure and that it

serves to prove the contention that a normal appearance should not deter one from removing the gall bladder if the symptoms and cholecystograms indicate disease and no other very definite cause can be found

There was no operative mortality

CASE REPORTS

Case 1 Mrs. B. Attacks of colic and pain in the R. U. Q. going to shoulder. Infected bile (biliary drainage) gas dyspepsia after meals. Perfectly normal appearing gall bladder without stones or adhesions. Appendix retro-cecal and adherent. Jackson's membrane. Inside of gall bladder showed thick velvety inflamed mucosa with tarry bile. I almost left this G. B. in as it was before cholecystograms. Convalescence was excellent and result perfect for 10 years followed

Case 2 Mrs. A. One attack during pregnancy 12 years before. Present attack, acute pain but not colic, for 5 days. Localized tenderness and muscle resistance. Less tender over course of colon. Gall bladder blue, no stones or adhesions. Appendix long, constricted in the middle and adherent at tip. Inside of gall bladder strawberry, with very dark bile. Perfect relief. Died 4 years later, calcinomatosis

Case 3 Miss H. M. (37 years old). For 1½ years severe attacks of pain, vomiting and fever. Localized tenderness and rigidity. Gall bladder normal in appearance, color and consistency. Enlarged glands along cystic duct. Congenital membrane between hepatic flexure and pylorus. Inside of gall bladder strawberry with single cholesterol stone. Result perfect for 12 years followed

Case 4 Mrs. E. H. (34 years old). For six months had attacks lasting a week of epigastric distress, discomfort to back and shoulders, acid stomach and soreness over gall bladder. No tenderness or rigidity at first examination. Operated one week after another mild acute attack with temperature 99 and leucocyte 9532. Gall bladder thin and very little off color. No stones or adhesions. Inside, a typical strawberry. Traced 12 years. Perfect relief

Case 5 Miss C., age 50. Attacks of colic for 20 years. Severe pain under xiphoid with voluntary vomiting. Tender over gall bladder. Gall bladder was thin and blue but packed with stones. Subacute hepatitis and a kinked appendix. Result perfect—15 years

Case 6 Mrs. L., age 48. For 8 months gas and intermittent colic. No tenderness or muscle rigidity but gall bladder seemed palpable. Cholecystography (vein) showed no filling. Right iliac tenderness. Gall bladder was blue, soft but the cystic duct was quite large without evident cause. Appendix bound down by bands. Result excellent—4 years

Case 7 Miss B., age 48. For 6 months had gas and a hunger discomfort. No colic. Has had fever. Soreness and pain in the right iliac. Perfectly normal appearing gall bladder but the omentum was adherent. Appendix was long with developmental abnormality of the mesentery and bands about the base. Examination of gall bladder specimen showed localized inflammation with inflammatory pathways extending along the blood vessels (very early, grade one, cholecystitis). Excellent result—10 years

Case 8 Mrs. H., age 60. Over 3 year period had 5 attacks of colic with no trouble between. Tender over epigastrium and gall bladder, without rigidity. Cholecystogram (vein) No filling. Gall bladder blue and thin and no stones. The omentum was adherent and the gall bladder bound to a dilated duodenum. Chronic hepatitis. Pancreas thick, hard and granular. Appendix sclerotic. Result perfect—10 years

Case 9 Mrs. M. G., age 47. "Indigestion" for several years with several attacks of colic. Tenderness and

stiffness over gall bladder. Cholecystogram (vein) normal. Gall bladder appeared blue and tense but not thickened. No adhesions. Appendix out. Specimen showed many small stones that could not be palpated before removal. Convalescence stormy with phlebitis. Good result but only followed 6 months.

Case 10 Mrs. M. S., age 42. For 5 months pain from xiphoid to shoulder. Occasional colic and some general abdominal cramps. Gas. Slight general abdominal tenderness, greatest over appendix and gall bladder. Cholecystograms (vein) inadequate function. Gall bladder normal in appearance, blue, thin and no adhesions. Appendix thick and congested. Ileal band. Specimen showed small, soft, very early, not palpable stones. Result perfect—1 years.

Case 11 Mrs. A. J. L., age 27. For 2 years gas and attacks of pain in gall bladder region without real colic. Tender right iliac and left upper abdomen. In upright tender under right costal margin. Cholecystogram (vein), no filling. Gall bladder blue and thin but intra hepatic being buried in the liver with three tongue-like lobes about it. Some chronic hepatitis. Appendix sclerotic. Result, 4 years remarkable relief of all digestive symptoms but did develop alcoholism and nervous disturbances.

Case 12 Mr. R. C., age 42. For 10 years gas and nausea. No colic nor even much pain. Localized muscle stiffness. Cholecystogram (vein) pathologic. Gall bladder was blue, thin and without stones or adhesions. There was moderate hepatitis and adhesion of duodenum to lower border of liver. Appendix had been removed. Result excellent—11 years.

Case 13 Miss M. M. S., age 52. For several years gas, heartburn and soreness in gall bladder region. One attack of colic. Cholecystogram (vein) pathologic. Gall bladder, blue except one yellowish spot, thin, no stones or adhesions. Appendix cord-like. Fibroid uterus. Specimen, typical strawberry. Result, some indigestion and pains in gall bladder region for over a year, then perfect relief for 10 years.

Case 14 Mrs. G., age 59. For many years abdominal pain and indigestion without colic. Of late pain had localized more to gall bladder and tenderness. Cholecystogram (vein) no filling. Gall bladder, blue, thin, without stones or adhesions, but the omentum was adherent to the cystic duct. Slight localized hepatitis. Appendix thick and manifestly diseased. Result excellent—9 years.

Case 15 Mrs. H. W., age 54. For a year, gas, dizziness, nausea and vomiting. No colic or marked pain. Tender over course of colon and in the upright over gall bladder. Cholecystogram (vein) pathologic. Gall bladder blue, thin, with omentum and duodenum adherent. Appendix thin and atrophic. Specimen one imbedded stone in cystic duct (not previously felt). Result. For several months a few attacks like common duct then perfect for 8 years.

Case 16 Mrs. J., age 48. For many years feeling of load in stomach, gas, dull epigastric pain going to right shoulder and several attacks of diarrhea. Several colics. Several attacks of right iliac pain. Has had temperature to 101. Tender over colon only. Cholecystogram (oral) borderline, probable pathologic. Gall bladder, blue, normal consistency with omentum markedly adherent. Appendix diseased with fecaliths. Result excellent except for large post-operative hernia. Followed 5 years.

Case 17 Mrs. U., age 38. For 9 months had epigastric pressure, nausea, heartburn, epigastric pain and one attack of possible colic. Cholecystogram not made. Gall bladder had normal appearance but omentum and colon adherent. Chronic diseased appendix. Small cystic ovary. Result. Immediate relief. Only traced for few months.

Case 18 Mrs. D., age 44. For 3 years pain in pit of stomach, much gas, headache and vomiting. No colic. Cholecystogram (oral) no filling. General tenderness over abdomen. Gall bladder thin, blue. No stones nor adhesions but a yellowish, hour glass, band one inch from fundus. Appendix normal. Result. Very poor. Traced 1½ years. Many complaints.

Case 19 Mrs. R., age 60. For 10 years attacks of colic with pain to right shoulder, every 4 or 5 months. Tender right costal margin. McBurney's and at angle of right scapula. Cholecystograms not made. Gall bladder blue, very slight thickening. Adhesions to duodenum and omentum. Two stones in cystic duct. Sub-acute hepatitis. Appendix not examined. Result. Perfect, only traced several months.

Case 20 Mrs. J., age 37. For 17 years had indigestion and dull pain in the upper epigastrium. Had been colic but not for 7 years. Fear of eating. Gall bladder tender but no rigidity. Cholecystograms. Called "normal" by radiologist, "pathologic without stones" by V. Gall bladder blue, soft but lusterless. Adhesions about cystic duct. Sub-acute hepatitis. Fibroid uterus. Specimen, strawberry gall bladder. Result. Markedly improved but occasional upper abdominal pain. Followed 7 years.

Case 21 Mrs. R., age 54. Years of indefinite symptoms, gas, dyspepsia, headaches, subicteric. No colic. Upper right rectus stiff. Gall bladder and colon slightly tender. Cholecystograms. Normal (radiologist), pathologic without stones and with hepatic flexure adherent (V). Gall bladder blue, soft, long and narrow with hepatic flexure adherent. Slight hepatitis. Jackson's membrane about ascending colon. Result. Very poor. No improvement in complaints.

Case 22 Mrs. B., age 33. Six months of gas and full discomfort. Colicky pains but not real colic. Forced vomiting. Cholecystograms pathologic with stones. Gall bladder normal appearance and consistency but with stones. Sub-acute hepatitis. Result. Perfect 6 years.

Case 23 Mr. T., age 42. For 6 months gas and dull pain in upper right quadrant. No colic. Right rectus stiff and localized tenderness over the gall bladder. Cholecystograms. Impaired function. Gall bladder blue, thin, no stones. Few adhesions about cystic duct. Sub-acute hepatitis. Pylorus thick but no stippling. Appendix out. Result. Relieved completely but only traced two months.

The following cases showed only slightly discoloration of the gall bladder.

Case 24 Mrs. W. B. K., age 52. Complained for many years of gas and a feeling of a lump in gall bladder region about one hour after meals. Tender gall bladder especially in upright. Biliary drainage pathologic. Gall bladder very slightly discolored, soft. Few, fresh adhesions. Definite pathology of mucous membrane. Result. Excellent for abdomen. Later developed myxoedema and psychoneurosis.

Case 25 Mrs. G., age 35. For many years heartburn and indefinite abdominal pain. Colon tender. Cholecystogram (vein) no function. Gall bladder blue except slightly yellow near the liver. Soft. No stones or adhesions. Appendix out. Result. No improvement.

Case 26 Mrs. N., age 48. For years had indefinite upper abdominal discomfort and fullness with gas. No colic. Gall bladder tender. Slight rigidity. Right iliac tender. Cholecystograms (vein) no function. Gall bladder blue with yellow streaking very slightly thick. No stones or adhesions. Marked chronic hepatitis, almost hob-nail. Sclerotic appendix. Result excellent 6 years.

Case 27 Mrs. F., age 36. For 2 years epigastric pain, belching, choking and painful spot in back. No colic. Persistent upper right abdomen and tender gall bladder,

feeling like a mass Temperature 99 Leucocytes 15,760 Cholecystogram pathologic Gall bladder very slightly off color and slightly thick No stones or adhesions Specimen strawberry Appendix normal Result Bad, all sorts of neurotic symptoms for 2 years

The last 5 cases had some absence of luster

Case 28 Miss P, age 53 For 12 years pains under right costal margin with gas and attacks of colic There were nausea, vomiting, diarrhea and slight jaundice with attacks General abdominal tenderness and temperature 99 Cholecystograms Atonic, poor functioning Gall bladder blue, lusterless, very slightly thick with no stones or adhesions Result Marked improvement Later developed hyperthyroid and return of diarrhea

Case 29 Miss M age 52 25 years' duration of pain in pit of stomach worse after meals with a crushed feeling under the right costal margin Gall bladder tender in upright only Cholecystograms normal Gall bladder blue, lusterless, normal consistency Specimen showed a small imbedded stone not previously felt Appendix chronic with fecaliths Lane kink Result Cure for abdomen Neurotic and orthopedic trouble, 3 years

Case 30 Mr H, age 39 "Bilious attacks" for several years One sharp colic from epigastrium to shoulder Subicteric Tender gall bladder and appendix Cholecystograms normal Gall bladder very slightly off color and lusterless, soft without stones or adhesions Appendix very long but rather normal Result Much improved but had 2 attacks of vomiting bile, probably migraine and an attack of pain in the gall bladder region 5 years later

Case 31 Miss H, age 26 For 2 months a dull epigastric pain worse on eating Nausea and vomiting Culminated in acute attack of fever and 15,750 leucocyte count There was general abdominal tenderness Rigid and tender over the gall bladder Cholecystograms Poor function Gall bladder blue, lusterless, thin, with colon adherent Specimen strawberry Chronic appendix with fecaliths Result 1 year perfect

Case 32 Miss N, age 54 For 18 months colicky pains in the upper epigastrium Slight tenderness to firm pressure over gall bladder Muscles equal Cholecystograms "Normal," radiologist, "pathologic with adhesions and deformity" (V) Gall bladder blue with slight yellow discoloration, lusterless, thin No stones or adhesions Slight hepatitis Appendix adherent Result Excellent Later developed cancer

ANALYSIS OF GOOD RESULTS

It has been said that (1) the more marked the pathology, (2) the longer the symptoms and (3) the history of colic is most apt to result in satisfactory results of cholecystectomy While from a practical standpoint these facts may hold true they are not based upon any sound reasoning certainly in the case of the first two The presence of typical colic makes far more certainty of diagnosis perhaps than any other thing so that it is easy to understand that in this group, with fewer mistakes in diagnosis, the cures should be higher

These cases were exceptionally well studied from a gastro-intestinal standpoint, many being followed for long periods of time before the operation, as well as afterward None were operated upon for a single sign

such as positive choleevstograms and none as pure exploratories, but only after mature judgment This may help to explain the high percentage of very satisfactory results

The appendix was removed in 12 of the 32 cases In several it was manifestly diseased and it is possible that some of the cures may have resulted from this as much or more than from the cholecystectomy However it is my belief that the appendix was not a factor in the majority of the cases

Analysis of the duration of symptoms failed to show any consistent difference between the perfect, the excellent and the poor results All groups contained patients whose history covered from 6 to 10 years or over

All cases which had colic recovered satisfactorily Of seven strawberry gall bladders, six gave good results but it is my impression that this type presents rather more in the way of morbidity and slower improvement than others

ANALYSIS OF POOR RESULTS

Cases 18, 21, 25 and 27 were unimproved The first three were more or less neurotic and perhaps the result might have been anticipated on this ground However it must be admitted that there were plenty of nervous patients in the improved group Case 18 had a history of 3 years but no colic There was no concentration of the bile and an hour glass gall bladder was present I would have expected a good result Case 25 in spite of a non-functioning gall bladder might as well not have been operated upon

Case 27 was an acute strawberry cholecystitis which should have had an excellent response to removal It is true that she was cured of the inflammatory condition as there were no subsequent attacks of fever or leucocytosis but she had protean symptoms for the two years that she was traced

SUMMARY

32 cases of relatively normal appearing gall bladders have been removed and the results traced for years

The surprising percentage of 87.5% of satisfactory results were obtained without operative mortality

Analysis of the symptoms and signs is presented together with analysis of the good and bad results

CONCLUSIONS

(1) It is perfectly possible to get as good results from cholecystectomy in properly chosen cases of relatively normal appearing gall bladders as in the more manifestly diseased gall bladders

(2) The patients must be carefully studied and operation decided upon only after mature judgment

(3) Symptoms and tests should correlate

(4) If the symptoms and tests warranted operation and no other satisfactory cause can be found at operation it is not only perfectly justifiable to remove the gall bladder even if it looks fairly normal, but excellent results may be anticipated

Notes On Nutrition

Frank G. Boudreau, M.D., Chairman, Food and Nutrition Board, National Research Council, in the March issue of *Nutrition Reviews*, points out that food itself and the science of nutrition stand as really basic factors in international relations at this time. "In parts of Europe and Asia food is the first thought of millions of human beings when they wake in the morning, craving for food accompanies them throughout the day and food is the subject of their uneasy dreams during the night." Nutritional rehabilitation will be the first duty of the United Nations in every country from which the enemy has been driven out, because this policy will assuage the civil disorder which otherwise is inevitable. Boudreau remarks that something was wrong with the civilization which, at the time of the financial depression, saw hunger and at the same time overstocks of food. International co-operation is the only answer to economic chaos, so that each nation may sell its surpluses of foods needed by other buying nations. The advances in nutritional studies which featured the decades since the last war showed that, as a rule, as income declines, diets became less and less complete, so that infant mortality and total morbidity varied directly with income. There exist several standards of dietary requirements and all are reliable, but actually people as a whole are not getting minimum requirements, as judged by any of these standards. In the U.S.A. we need the following increases in production to make the standards possible—meat 5 per cent, eggs 20 per cent, milk 80 per cent, citrus fruits and tomatoes 40 per cent, vegetables 180 per cent. Freer international trade can solve many nutritional problems which national self-sufficiency cannot solve. Stabilization of agriculture on a world wide scale would do much to stabilize world economy, since 60 per cent of the world's population are farmers and 90 per cent of agriculture is devoted to food production. The various freedoms would be served by a highly organized international nutritional and agricultural study and policy.

Wheat Proteins Although it has been shown that whole wheat flour possesses better protein than white flour, yet the substitution of the former for the latter would not take care of the severe protein shortage caused by the scarcity of meat and milk, which are our best sources of protein. There is a small difference in the digestibility of white and whole wheat flour (*Lancet*, I 319, 1942) favorable to the former. The proteins in whole wheat flour are of better biological value than those of white flour (*Lancet*, I 405, 1942), but flour of any kind did not produce the excellent biological values of proteins derived from casein. While the proteins derived from wheat do not possess the biological value of proteins from animal sources, they do, however, form a valuable contribution to the diet.

Fluorides and Spinal Deformities in Man Fluorosis produces mottled enamel in teeth, and in a region in England in which such mottling was common and due to the mineral constitution of the water, many persons having mottling were examined for skeletal changes and it was felt that an unusually high per cent of

spondylitis deformans (hypertrophic spinal arthritis) was associated with the dental condition, which suggested, but can scarcely be said to prove that fluorine in the diet may have a destructive influence upon bone metabolism (*Lancet*, II 93, 1942).

Dietary Fat and Fatty Livers How much liver infiltration by fat can occur as a result of eating fats? As a result of experiments in which rats were fed various proportions of saturated and unsaturated fats and oils it was concluded that the fats chiefly responsible for dietary liver infiltration are those whose constitution is represented by C14 to C18 and which are saturated. Solid unsaturated fatty acids produced no such effects. Possibly one should conclude that the ingestion of excessive amounts of edible saturated fats and oils is contraindicated. What about butter? The experiments did not show that actual disease of the liver was produced by fatty infiltration resulting from dietary excess.

Histidine, Histamine and Toxemia of Pregnancy Probably there is a real connection between toxemia of pregnancy and the metabolism of histidine and histamine, because histidinuria normally present in amounts of from 15 to 50 mg per cent in normal pregnancy, practically disappears in pregnant women in the preeclamptic toxemia. The finding of a reduced excretion of histidine in the urine is, in fact, a valuable sign of impending toxemia (*Biochem J*, 35 213, 1941). Just what causes this decrease is not as yet certain. There are two enzymes which can change histidine to histamine—histaminase and histidine decarboxylase, and histamine may be found in the urine in severe toxemia of pregnancy. A restriction in the meat and egg consumption of these cases has been suggested but the general opinion is that until more is known about the histidine metabolism, such restriction is not justifiable and may even be harmful.

Ascorbic Acid and Phosphatase Activity Experiments on guinea pigs showed that dietary ascorbic acid stimulates alkaline phosphatase production in the blood, and that ascorbic acid does not merely activate the existing alkaline phosphatase present in the blood (*J Nutrition*, 23 271, 1942).

B-vitamins and Neuropathology Neurologic manifestations invariably accompany dietary deficiencies of the Vitamin B-complex, varying from ataxia to convulsions. A lack of thiamine results in histopathology of the peripheral nerves, although it has been shown that thiamine lack does not invariably result in peripheral nerve disease. Other Vitamin B components now are under suspicion as being capable through deficiency of producing neurological changes (*J Nutrition*, 16 451, 1938). Of these riboflavin deficiency causes degeneration of the myelin of the main peripheral nerve trunks. Likewise pantothenic acid was found to be essential for the preservation of normal growth and development of the spinal cords of chicks (*J Nutrition*, 18 227, 1939). The spinal cord and peripheral nerves of rats were affected by deficiency in riboflavin (*J Nutrition*, 22 345, 1941). Sensory neurone degeneration occurs in growing pigs when

either pyridoxine or pantothenic acid or both are lacking in the diet (J Nutrition, 24 345, 1942) A subacute inflammation of the colon occurred when pantothenic acid was lacking in the diet In the absence of pyridoxine in the diet, fatty livers developed

Citrus Fruit Juices and Calcium Assimilation The effect of citric acid-citrate mixtures on calcium assimilation were undertaken and it was found that orange juice did something which the citric acid-citrate mixtures did not do—it contained some unknown substance, in addition to citric acid and citrates which favored calcium assimilation (J Nutrition, 23 293, 1942)

Cardiac Failure in Chronic Thiamine Deficiency Both clinical and animal investigators agree that cardiac failure in chronic thiamine deficiency depends on two factors impairment of myocardial function and marked vasodilatation (Ann Int Med, 17 645 1942) Arch Int Med, 70 763, 1912) Recovery is dramatic on the administration of thiamine Clinically the condition is most likely to be met in chronic alcoholism

Vitamin A Not Effective in Hypertension The original report that Vitamin A had an effect in large doses of lowering elevated blood pressure in "Goldblatt dogs" (those whose renal arteries were reduced in caliber) is now contradicted by the same authors (Proc Central Soc Clin Res 15, 1942) who found that a highly purified Vitamin A had no such effect The pressure lowering effect previously obtained must have been due to other substances present in the solution which they used parenterally and which altered the pressor mechanism produced by renal artery constriction Now the problem is to find out what specifically was responsible Possibly the present clinical movement in the direction of using Vitamin A in hypertension should be held up for further information

Vitamin C Metabolism in Adults Individuals vary widely in the blood ascorbic acid values and in the urinary excretion of ascorbic acid as related to intake There may or may not be a sex factor in the explanation of differences in excretion noted in one set of experiments Plasma levels of ascorbic acid seem to have a characteristic of their own for each individual, without sex difference High plasma levels indicate adequate tissue levels and low plasma levels are usually associated with tissue depletion (J Nutrition 23 111 1942) After the ingestion of ascorbic acid in crystalline form or in food form with breakfast there was a gradual increase in plasma levels following the meal reaching its maximum about 90 minutes after breakfast and gradually returning to its fasting level For some persons 50 mg is regarded as a daily minimum and 75 mg as a satisfactory standard daily intake

Caloric Intake and Tumor Growth Two sets of experiments with mice seem to show that when the total calories of the diet are reduced by one-third there is much less likelihood of spontaneous tumor development or "takes" in transplanted tumors Clinically the book, Diet and Cancer by Hoffman is recalled, in which the general idea was developed that cancer victims have been good eaters It is not justifiable on the basis of these experiments to suggest that caloric reduction should be undertaken in the treatment or prevention of human cancer (Cancer Research, 2 460, 1942), (Surgery, 11 48, 1942)

Vitamin A Concentrates Affect Milk While it might be supposed that feeding cows shark liver oil and/or Vitamin A would increase the Vitamin A content of milk and butter fat, many experiments have shown that the amount of increase of Vitamin A in milk and butter by such feedings is inconsiderable in proportion to the large amounts needed to be fed to get a result and that shark liver oil seems to hasten the normal decline of milk production with the advance of lactation (J Dairy Sci, 25 931, 1942)

Mineral Metabolism in Man. Hemoglobin normally can be attained in children on a daily intake of 10 to 15 mg of iron (J Nutrition, 23 181, 1942) In young women about 11 mg iron per day served to make good the menstrual losses (J Nutrition, 23 229, 1942) Calcium retention is influenced by the diet The use of milk in amounts of a pint to a pint and a half per day in young adults coincided with calcium retention increase but this was partly due to the adequacy of the diet as a whole So far as calcium, phosphorus and nitrogen are concerned the old rule of a pint of milk per adult and at least a quart per child per day is sound nutritional practice (J Nutrition, 24 367, 1942)

The Etiology of "Alcoholic" Polyneuropathy The use of crystalline thiamine in treating alcoholic neuropathies in association with a high Vitamin B diet has had only a limited degree of success, possibly because the alcoholic suffers also from deprivation of other vitamins as well and this thesis becomes increasingly likely as we realize that Vitamin A and Vitamin C and various members of the B-group also are needed to preserve neural normality The partial failure of the thiamine therapy may be because many neuropathies are infectious in nature The estimation of blood pyruvate following glucose ingestion is of value in estimating the blood and tissue lack of thiamine Cases showing normal fasting amounts of pyruvate may tentatively be regarded as suffering from an infectious neuropathy rather than a thiamine deficiency (J Biol Chem, 133 585, 1940) Such tests are of value only in the acute stages of thiamine deficiency In chronic cases of neuropathy we are dealing with residual anatomic lesions, and in these cases the thiamine blood levels are within normal limits (J Biol Chem, 471, 1939)

Feeding Industrial Workers Obviously the war worker needs to be kept in a condition of health which will make it possible for him to remain in a state of peak production His nutrition is one of the important points which must be met, and is the one point which has received least consideration in the past Many dietary deficiencies exist among industrial workers, and each plant ought to have its own planned programs of nutrition for its own workers Good food is paramount but vitamin supplements are necessary too, especially for those who are subject to respiratory infections, who are over or under weight and who are under unusual nervous strain (Med Clin of N A, 26 1067, 1942) A cold meal containing well balanced food and vitamins is better than a hot meal not so balanced Frequent feedings rather than three big meals has increased production where it has been tried

Mechanism of Carotene Oxidation Carotene does readily oxidize but the mechanism does not seem to depend on fat oxidases Possibly unsaturated fat must

be in the process of oxidation to effect rapid carotene oxidation (J Biol Chem, 146 215 1942)

Iron Absorption in Man The intestinal mucosa probably acts specifically in deciding how much iron to accept and absorb and how much to decline, because maximum absorption occurs in those cases in which iron storage is at the lowest ebb. The studies based on the absorption of radio-active iron have made this point clear (J Exp Med., 76 15 1942)

Para-aminobenzoic Acid and Sulfonamide Drugs Para-aminobenzoic acid is one of the B-complex vitamins which has a blocking action on the sulfonamide drugs because e.g. para-aminobenzoic acid is structurally similar to sulfanilamide and a competition develops between the two substances for a site in the enzyme system of the bacterial cell (Brit J Exp Path., 21 74, 1940)

Renal Damage in Choline Deficiency Choline is an important dietary factor whose absence causes ex-

cessive lipids to be deposited in the liver, with involvement of the thymus and marked renal congestion with hemorrhage. In choline deficiency bizarre renal lesions such as symmetric necrosis develop and these resemble renal lesions seen in eclampsia (Arch Path 34 866, 1942)

Pyridoxine Therapy for Acne Vulgaris From 50 to 250 mg of pyridoxine orally per day brought about undoubted improvement in many cases of persistent and chronic acne. In many cases this use of Vitamin B6 showed marked improvement in a few days. While one must reserve judgment as usual this work is so well supported by clinical trial that clinicians would be justified in trying it (J Invest Dermat., 5 143 1942)

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Letters

2nd Field Hospital, Third Platoon
AP0928—P O San Francisco,
March 12, 1943
Somewhere in New Guinea

To the Editor

Thank you so much for your letter of November 12, 1942 only recently received. If I were still in practice in Rochester New York, I would have another contribution or two for you. Here in the "Field" it is difficult to contribute any specific work because of the fact that so many are involved with so little. As a civilian would say—"There is a certain amount of red tape" which takes away the enthusiasm of one interested in contributing specific material.

At present I am attached to a Field Hospital and am in charge of the surgical department. This is a highly mobile unit which is equipped to give all types of definitive medical and surgical care for prolonged periods. We have spent about eight months in the tropics and being in a combat area the volume of our work has been large and varied. A complete laboratory and X-ray department are attached to our unit so we have ample opportunity to study every case with the greatest care. Perhaps you would be interested in some of the things we have contacted and our reaction to them.

Vitamin Deficiency—inasmuch as there is little or no source of fresh fruits, vegetables, milk meat etc. there is a prevalence of deficiency states either partial or complete. This is most noticed in those who are in an actual fighting status and is especially marked in the prisoners who have frequently been for weeks on limited rations. Perhaps the most interesting deficiency problem was seen in the case of a 51 year-old male—a member of a small ship crew. For five months he had eaten nothing but tin rations which, in his case, consisted of beef ("bully beef") in its various forms and hard tack. No fruit juices or fresh vegetables were eaten. At time of admission he was suffering from dengue. He had a fever of 102 to 104 degrees for one week, during which time he refused to take more than water. On approximately his tenth hospital

day I was asked to see the patient for what appeared to be a surgical complication. He had a small abrasion on the sole of his right foot—just at the base of the 5th toe. The entire sole of the foot was dark and discolored and fluctuant. A similar picture was present in the left foot, but no abrasion was present. The patient was spitting up large amounts of fresh blood and complained of a raw sore throat. Examination showed hemorrhages from his gums, his posterior pharynx and mucous membrane of the mouth. Multiple small ulcerations were present in all of these areas.

A diffuse hemorrhage had taken place in the subcutaneous tissue and skin of the chest, back, forearms and legs. Petechial hemorrhages were present throughout the rest of the body. A small incision was made in the sole of each foot and a large amount of the old blood evacuated. A blood smear was negative for malaria or leukemia. Urine analysis revealed the presence of a few red blood cells. The diagnosis was obviously that of Scurvy, which had been precipitated in a subclinical Vitamin C deficient patient by the sudden onset of a fever (dengue).

800 mgm. of Vitamin C was given intravenously and fresh fruits were procured. The recovery was remarkable. The hemorrhage ceased in 6 hours, the patient's appetite returned, and he generally improved. The skin over the hemorrhage area exfoliated and a new healthy skin was found underneath. After 12 days of intensive vitamin therapy, the patient appeared nearly normal and was able to be up and around with new vigor.

The dentist reports that a great number of patients have bleeding spongy gums which respond to Vitamin C and B in combination.

There is no question that the wounds, tropical ulcers, burns, etc. heal much more rapidly in those individuals who have been on a good diet before treatment—in contrast to those who have been on an obviously deficient diet. For this reason we administer large amounts of multiple vitamins to all surgical cases. Also during their convalescent period the nervousness, malaise and inattention is frequently im-

proved by giving large doses of Vitamin B intravenously

As a routine measure all of our personnel receives multiple vitamin capsules (Lilly) three times daily, which we feel is definitely advantageous

On many occasions we have been asked to care for the natives both surgically and medically. On other occasions I have visited the native hospitals and observed the cases on hand. There is very little evidence of deficiency states among these primitive people. This is probably due to the fact that their diet consists of large amounts of polished rice, fresh fruits, such as paw paws, pineapples, bananas, lemons, oranges,

mangos, etc. They also raise radishes, corn, tomatoes, sweet potatoes, taro, sugar cane, cucumbers, and other vegetables. Their meat is chiefly pork, but this is eaten on only infrequent occasions. A great number of dysenteries are seen in these individuals, but in no instance have I seen a sprue type of diarrhea. They are for the most part due to hookworm or bacillary infestations.

I hope that these brief comments are of interest to you and others as you see fit.

Sincerely,

Leonard K. Stalker, Capt. MC

Clinical Excerpts

PROCTOSIGMOIDOSCOPY

My purpose in this short article is to direct attention to the fact that some gastro-enterologists do not employ proctosigmoidoscopy as a routine diagnostic procedure. My slogan, *that no general examination of a patient is complete without proctosigmoidoscopy*, has been employed in my practice since 1908. In 1915 I presented a paper before the Gastro-Enterological Association on the removal of polyp and malignant adenoma in the rectum and pelvic colon by means of the snare and cautery, as well as by an especially constructed guillotine. In 1930 I published my paper on Diathermy of the Rectum and Pelvic Colon, presenting 260 cases, pointing out that diathermy is the treatment of choice in pre-cancerous polyps, and small adenomacarcinoma that project into the lumen of the gut.

Finally I designed a $\frac{3}{8}$ inch caliber sigmoidoscope fashioned after the Strauss-Tuttle instrument for use in strictures of the rectum, and found it to be very valuable in vaginocopy in virgins. In the knee-chest posture a good view of the cervix can be obtained and polyps and early malignant growths easily destroyed by diathermy. Our records show hundreds of such cases. I formulated seven rules for the sigmoidoscopist:

1. Never use the inflation apparatus, because of the possibility of perforation.

2. Use plenty of lubricant and explore well with the index finger prior to introduction of the instrument.

3. Make all progress under guidance of the eyes and do not use any force. Use 25% solution of magnesium sulphate to relax spasm. Try pressure with the wet cotton applicator, and if not overcome, insert a soft rubber urethral catheter and inject two ounces of the solution.

4. Be sure the patient assumes the correct chest posture.

5. Employ a flat table. I never use the inclined plane or the Hanes table so much in vogue, because I found an inflation was necessary to introduce the tube, and inflation has produced perforation.

6. Make free use of the long wooden applicators correctly wrapped with cotton. I have frequently

located a growth which was high up in the sigmoid by having the applicator return repeatedly blood colored when the X-ray disclosed no diagnostic defect.

7. In dilating the rectal sphincter for spasm or stricture, make your pressure always upward toward the coccyx (in knee chest posture) thus avoiding the pain produced by pressing laterally or toward the perineum.

Horace W. Soper, St. Louis, Mo.

SUGGESTION ON A POINT OF REGIMEN IN THE THERAPY OF INTRACTABLE PEPTIC ULCER

The treatment of intractable peptic ulcer has been notably disappointing and unsatisfactory. This variety of ulcer runs a course of many years of almost constant pain and insomnia punctuated with hemorrhages.

The Sippy diet, as followed after a hemorrhage, will bring relief, and keep the patient alive with a minimum secretion of hydrochloric acid. Unfortunately this diet is inadequate to maintain the strength of a patient returning to active life. More substantial food is required, and the old vicious circle will soon reappear. Ingestion of food, secretion of hydrochloric acid and resultant hyperacidity, pain, ingestion of food, secretion of hydrochloric acid, hyperacidity, pain, and so on with a possible rest of a few hours in the early morning. There may be remissions of a few days or weeks, but when the ulcer flares up, the same sequence will recur.

The cause of intractable duodenal ulcer is particularly the insomnia caused by pain occurring around 1 or 2 o'clock every night for months and years. During those episodes (judging from my personal experience) there is nothing, no alkaline drug, no sedative, no antispasmodic that will break that vicious circle. I have tried them all, they give relief, but they are merely palliatives. It is like sprinkling water on forest fires around a volcano while the crater itself is still in full activity.

Gastrectomy is the only alternative. A man in the sixties, however, will think twice before he runs such a big risk. In view of the total failure of therapy, the sufferer from intractable duodenal ulcer may well be excused for grasping at any straw that might give him relief. It is with this idea in mind that I venture to offer the present suggestion.

In starting this section, Clinical Excerpts, all authors are invited to send in short articles similar to the above containing definite value in cases where they do not desire to write a long formal article.

who eat four times a day) is the thing that will break the vicious circle

At the onset this diet will be difficult for the ulcer patient who is inclined to eat a bite at all hours of the day to stop the hunger pain and silence the stomach. As a concession, in the beginning, 1 cup of milk at 6 p.m. may have to be allowed him.

In my experience, the foregoing diet of 2 meals a day, which may be called "part-time daily fasting," is ample to maintain the normal weight (170 lbs.) of a man doing light work (hospital rounds or operations) in the morning and office work in the afternoon. Whether it would be sufficient or would have to be modified for manual workers is a question that would require further study.

It may take several weeks for any one to accustom himself to this regimen. If the plan works the patient will notice two things: (1) that he will soon be able to sleep through the night without pain and without drugs, (2) the next day he will miss his familiar attendants of many years, the hunger pain in the late morning and late afternoon, this will be very slight or absent entirely.

Will a duodenal ulcer heal under this treatment? I doubt it, this lesion in its intractable form seems to defy any therapy. With the constant irritation and caustic action of the hydrochloric acid withdrawn

during the greater part of the time, however, the ulcer may have a chance to recede, as evidenced by improvement in the symptoms.

It remains to be seen how patients will take to such a rigid diet, some will consider it worse than a straight-jacket. The chief drawback is that a man will be shut off from much pleasant social life, which is built around evening dinners, banquets, etc. I should not suggest such a regimen to a patient with mild symptoms, knowing that he would not even give it a trial. It is up to the patient with severe symptoms to make his choice between two things: on one side conviviality and evening meals generally, with consequent pain and insomnia, or partial daily fasting with sleep and freedom from pain at night. I believe the real sufferer who has gone through years of distress, and especially insomnia, will try anything that gives relief and will soon become reconciled to such Diocesan procedures on the ground that of two evils the lesser one should be chosen.

I realize that the present communication, without laboratory experiments and without statistical data, may have little scientific value. However, as this one case has been well observed, I hope that some internists, better qualified than I am, may have occasion to try this plan in the treatment of intractable forms of peptic ulcer. Paul S. Campiche, San Francisco, Calif.

Editorials

EUTHANASIA

N articles appearing in the same Journal* (*American Jour. Psych., Vol. 99, No. 1, July, 1942), Foster Kennedy, M.D. and Leo Kanner, M.D., touch the problem of euthanasia. The former favors euthanasia under legal sanction in carefully defined cases, and offers some strong arguments in support of his position, but the latter opposes it on the grounds that an idiotic child may have fond parents who want him alive. The editorial writer in summing up the case seems to feel that no law will be passed until public opinion favors euthanasia and that the nucleus of such public opinion will be the attitude of the parents of idiots. He feels that in evaluating and meliorating the parental attitude, the psychiatrists' interest in the whole question must center.

This is a very different attitude from that in which euthanasia by edict becomes merely an instrument of power in the hands of the state. Presumably what is meant is for the state to permit the painless death of idiots in cases where the parents desire it. The role of the psychiatrist would be in helping the parents to think logically, and to make decisions which would not leave them dejected by later remorse or sense of guilt.

The state would be in effect saying: "This idiot is of no value to the state and the state is only too happy to be rid of the idiot, provided his death is agreed to by the parents." In such an interpretation of a law permitting euthanasia, the state reveals an attitude of making its desire conditional upon consent and such a law would perhaps lead to a modification of the law in which the urgency of euthanasia must not be conditional upon anything except a medical certificate of idiocy.

But if legal sanction be regarded merely as state's permission to commit euthanasia in cases in which parents desire it, the state might more easily modify the law to permit euthanasia for disabling feeble-mindedness, should the parents desire it.

The desire of parents to have an idiotic child killed may range from pity to pride and may mask itself under many guises. Presumably the psychiatrist would be employed to determine the genuineness of the parental motive, and this would impose on a medical man a very undesirable responsibility.

It seems questionable if we shall ever intellectually come any closer to an evaluation of the two tremendous ideas involved in euthanasia—life and death. Our attitudes today are built upon authoritarian teachings, superstitions and the intuition, with very strong moral respect for life, and a decidedly mechanistic and nihilistic attitude toward death. Our agreement upon the positive worth of life and the right to live one's life is so essentially a part of our democratic idea, that its ablation in even one specific instance may do harm to the inviolateness of the ideal. If the ideal is really inviolate, then the state ought not to permit even the parents of an idiot to decide the idiot's death. If the state feels that it has a role in keeping the genetic strains pure, it should make the law mandatory upon a physician's certificate of idiocy, and should not consult the parents. If it does this, however, it becomes decidedly undemocratic and totalitarian.

Then there is the question whether medical men should be granted direct authority in deciding death or in inflicting death. Already indirect power is theirs in jurisprudence in cases where sanity is

questioned, but do they want direct power or the job of executioner? Killing an idiot gets rid of parental nuisance and, provided the parents do not succumb to a life-long remorse, they will be freer to do what they want to do but will their path in life after the euthanasic death of their child lead them to anything more valuable than the experience of caring for a defective? If we regard material expansion as the ideal, then the answer is yes. If we regard moral and spiritual development as paramount, the answer probably is no.

Finally, since we know nothing about the value of a life which is intrinsically sealed by idiocy against our efforts to decipher it, we might perhaps be wise to choose the ancient law of Moses and refrain from killing even under the most refined conditions of rationalizing efficiency.

ROENTGENOLOGY OF THE SMALL INTESTINES IN NUTRITIONAL DISTURBANCES

THE roentgenology of the small intestine has been one of the main topics of the field of roentgenology in gastro-enterology. Among the outstanding publications is the Carman lecture delivered before the Radiological Society of North America, in 1940. The studies made by Golden were so exhaustive that since that time practically nothing new has been heard in this field. The author reported his findings of abnormalities of the small intestine in the nutritional disturbances. We would like to draw attention to this excellent publication, for it covers not only the roentgenological findings, but also the pathological-anatomical findings in these rare conditions. Such exhaustive studies can only be made when the author has a staff of such well trained cooperators at hand, as Golden had in those men working in different departments of the Presbyterian and Babies Hospitals in New York. In addition, he made a most thorough study of the literature covering this interesting field.

Certain nutritional deficiency states, in both early and late stages, are associated with disturbances in the motility and mucosal pattern of the small intestine recognizable by roentgen examination. When no obvious anatomical reason for their existence is apparent, they may be classified as primary, and when they are associated with some organic disease of the gastro-intestinal tract, mesentery, liver or pancreas, they may be described as secondary.

Pathological changes in the intestinal wall occur as a result of long continued nutritional deficiency, but seem to vary markedly in different individuals. There is strong evidence of damage to the intramural nervous system. The earlier changes are undoubtedly reversible, but if the condition persists long enough, the intestine may be permanently damaged. Under adequate treatment, the middle region of the small intestine does not seem to be restored to normal as rapidly as the proximal region, the former may show persistent evidence of damage after the latter appears normal, and after the patient is clinically well.

The clinical as well as the pathological manifestations are variable. The symptoms are often obscure or misleading. They may complicate a condition requiring surgical treatment.

Associated with the objective changes in the small intestinal pattern disturbances in the physiology of

absorption occur which suggest that the small intestine may be part of a vicious circle, for the interruption of which, parenteral treatment may be necessary.

Golden points out that objective changes in the small intestinal pattern, similar to those occurring in vitamin deficiency, have been associated with clinical and experimental hypoproteinemia and several other conditions.

The roentgenological findings in deficiency states involve motility, and the outline of the loops as well as the mucosal pattern of the small intestines. Golden remarks that those changes seem to be most pronounced in the region of the middle third of the gut, whereas the terminal ileum, for some reason, seldom appears abnormal. The motility may be increased or decreased, and the intestinal loops may be distended or contracted. The mucous membrane may show coarse folds in some cases, whereas, in others, an obliteration of the folds has been seen. Until now, we do not know what particular pathological conditions cause one or more specific changes in the roentgenological outline. Here is a tremendous field which has to be thoroughly studied. Hyper- and hypo-motility of the small intestines surely cannot be caused by the same conditions.

Of the greatest importance is the fact that exactly the same type of intestinal pattern as that found with well advanced deficiency states, is present in normal newborn infants, which after three or four months is replaced by the usual adult pattern. This change is probably due to the evolution of the incompletely developed nervous control of the intestine.

It would seem that some common mechanism must operate in the production of these phenomena from so many different causes. A possible, if not the most probable, mechanism is the interference with or damage to the intramural nervous system of the intestine.

Although a positive differential diagnosis cannot be made, the detection of these abnormalities of the small intestines on roentgen examination will serve to draw attention to the possibility of a nutritional deficiency and may lead to its correction before serious damage is done.

We would not be astonished if the coming years would permit us to make exhaustive studies, based on material such as people in prison camps, who, unfortunately, have been on a vitamin deficiency diet for a long time.

Franz J. Lust

LITERATURE

Abnormalities of the Small Intestine in Nutritional Disturbances. Some Observations on Their Physiologic Basis (Carman Lecture) Ross Golden. *Radiology* 36:262-286 March 1941.

ERRATUM

The second paragraph of the Summary of the article "The External Secretion of the Pancreas and Diabetes Mellitus" by Pollard, Miller and Brewer, which appeared in the January issue, should read "The observed deviations from the control group of eight patients were diminutions in volume of secretion and total secretion of bicarbonate and the enzymes, amylase and trypsin" instead of four patients as stated.

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CLINICAL MEDICINE MOUTH AND ESOPHAGUS

YOUNG, D *Esophageal-hiatus Hernia Rev Gastro-Enterol*, 9 345, Sept, Oct, 1942

Esophageal-hiatus hernia is the most common type of diaphragmatic hernia and is frequently diagnosed as other forms of organic disease. It is generally classified as (1) short esophagus type, (2) paraesophageal type, and (3) all other hiatus-hernias. Factors influencing the formation of these hernias vary from local tissue change to alterations in intra-abdominal tension. The symptomatology depends upon mechanical interference with the function of the herniated organs or pressure on those organs encroached upon within the thoracic cage. Some simulate peptic ulcer, others angina pectoris, gall bladder disease, dysphagia syndrome, obstruction, unexplained secondary anemia and finally the large asymptomatic group. A radiographic examination is necessary to establish a positive diagnosis. Methods practiced roentgenologically designed to disclose most accurately the lesion are here described in detail. The complications reflect the mechanical influences of esophageal-hiatus hernia and include obstruction, strangulation, ulceration, hematemesis, stricture, anemia and nutritional abnormalities. Therapy is generally medical with frequent small bland meals, weight reduction, rest, sedatives, antispasmodics and anti-anemic preparations. Phrenic nerve block is a valuable and palliative procedure while more radical surgery is indicated in a selected group of complicated cases.—Michael W Shutkin

STOMACH

JUDD, E S, JR *Residual Lesions of Ulcerative Gastritis S G O*, 75 424, Oct, 1942

In this article the author attempts an evaluation of the relationship between changes in the gastric mucosa and gastric cancer. The literature on gastric carcinoma is given at some length. Dr Judd feels too much attention has been given to gastritis as a cause, and that greater interest should be centered on long-standing lesions of the gastric mucosa. In this investigation he examined microscopically specimens from 200 carcinomatous stomachs and 78 average stomachs. The residual lesions of ulcerative gastritis were "irregular thickening and fibrosis of the muscularis mucosae, atrophy of the chief and parietal cells, hyperplasia of the mucous cells and disorganization of the mucosal elements." The frequent occurrence of such lesions in carcinomatous and non-carcinomatous stomachs is compared. Atrophy and hyperplasia seemed to be the 2 significant residual lesions. The author suggests the hypothesis that atrophy of the chief and parietal cells initiates an attempt at repair by hyperplasia of the mucous cells. Control of the hyperplasia is lost, and cancerous growth develops. It has not been proved that achylia is a cause of cancer. In conclusion, Judd states that the main difference between normal and carcinomatous stomachs is the absence of mucous cell hyperplasia in

the former. The most important factors in carcinoma are (1) many years of anatomic insults resulting in residual lesions and disorganization of the reparative processes, (2) age, (3) heredity. Gastric carcinoma develops over a long period of time before its clinical manifestations, and it occurs in a previously damaged stomach.—Francis D Murphy

DOEHRING, P C AND EUSTERMANN, G B *Association of Pernicious Anemia and Carcinoma of the Stomach Arch Surg*, 45 554, Oct, 1942

The average duration of life for the patient with pernicious anemia before the introduction of liver therapy in 1926 was 5 years, and this short interval did not permit many complications to develop. Carcinoma of the stomach, however, was often found. Here the authors give a brief review of past reports on the association of carcinoma of the stomach with pernicious anemia and state that the early writers felt that pernicious anemia predisposed a patient to carcinoma of the stomach.

In this paper, the authors record the results of their observations on 40 patients with associated pernicious anemia and carcinoma of the stomach studied at the Mayo Clinic. Of 1,014 cases of pernicious anemia, 17 had carcinoma of the stomach, this is an incidence of 1.7 per cent or slightly higher than the incidence of gastric carcinoma in the general population. Carcinoma associated with pernicious anemia was found to be of a similar grade of malignancy and in the same situation as carcinoma uncomplicated by pernicious anemia. Pernicious anemia usually sets in at about the age of 54.5 years, while signs of cancer appear at the age of about 63.2 years. Gastric carcinoma in association with pernicious anemia is becoming more common, probably due to the fact that modern methods of treatment prolong the period of survival long enough for carcinoma to set in. Achlorhydria is invariably found with pernicious anemia and usually with gastric carcinoma. The cancer usually develops in the pyloric region. It develops with less frequency in the middle third of the stomach, and is most rarely discovered in the upper third. All the cases studied here were adenocarcinoma. Benign tumors or polyps develop rather often in cases of pernicious anemia. The relationship between the two diseases is discussed briefly. Present evidence is insufficient to prove a direct connection of these disorders, but there is reason to suspect that persons with pernicious anemia are more likely to develop gastric carcinoma than the normal person.—Francis Murphy

BOWEL

ROWE, P G *Intussusception in Adults Can Med Ass'n J*, 47 219, Sept, 1942

Previous reports have shown that approximately 78.5 per cent of the cases of intussusception occur in children under two years of age and that from 5 to 10 per cent of all the cases occur in adults. This paper reports 10 cases of intussusception in adults.

All cases of intussusception are classified into primary and secondary groups. The former includes all cases in which no causative lesion can be found while the latter embraces those in which some primary lesion can be demonstrated as the cause. In children, most of the cases are of the primary type while among adults the majority of cases belong to the secondary group. Primary intussusception usually starts at the ileocecal junction. Among the theories advanced to account for this are excessive mobility of the caecum and ascending colon, the action as a foreign body of excessive lymphoid tissue found in the lower ileum, the marked protrusion of the ileocecal valve into the caecum, the incoordination of the muscular coats in the lower ileum, incoordination of the autonomic system and dietary indiscretions and excessive purgation. Secondary intussusception is due to such primary lesions as intestinal tumors, ulcerations of the intestinal wall, Meckel's diverticulum and a few other more rare conditions. Most intussusceptions are of the isoperistaltic or descending type but retrograde or ascending intussusception does occur. The method of production is essentially the same in both types. Retrograde intussusception is relatively infrequent only one case occurring to about 100 of the other. Retrograde intussusception may occur anywhere in the gastro-intestinal tract from the stomach to the sigmoid. Combined ascending and descending intussusception may occur as well as retrograde intussusception of the jejunum into the stomach through a gastro-enterostomy stoma. The latter complication does not take place until from 5 to 15 years after the gastro-enterostomy and is thought to be due to a too rapid expulsion of acid gastric juice resulting in a violent reverse peristalsis from irritation. The symptomatology of intussusception is discussed under three headings: acute, chronic and recurrent. The 10 case histories follow.—Ira Manville

BOWER, L. L. *Constipation—Its Management* *Rev Gastro-Enterol*, 9 366, Sept., Oct., 1942

Functional constipation is widely distributed among humans. The more common causes include lack of adequate exercise, neglected defecation reflex, laxatives, faulty diet and insufficient fluid intake, and other less important influences. A correct diagnosis should be established only after a thorough roentgen and sigmoidoscopic examination. Twenty-five ambulatory cases were studied and followed for two years. Treatment prescribed a regulated diet including raw and cooked fruits, meat and green vegetables, regular relaxation and exercise, daily habit, and adequate vitamins, minerals and water. After two years, 18 had normal bowel habits, three took bulk producers, and 4 were failures. In the treatment the necessary principles are (1) regular daily habits of exercise, rest and morning visit to the bathroom, (2) a well balanced diet of meat, fruits and vegetables, (3) vitamins, minerals and adequate fluid intake.—Michael W. Shutkin

KANTOR, J. L. *The Sprue Syndrome* *A Symposium* *Rev Gastro-Enterol*, 9 335, Sept., Oct. 1942

The sprue syndrome is predominantly an absorption defect involving the upper small intestine and is found distributed through all age groups. The wide variety of etiological factors fails to explain the disturbance in fat and carbohydrate absorption, followed by steatorrhea and diarrhea. The chemical union of split fatty acid with enteric calcium salts results in hypocalcemia and nerve irritability with local and constitutional manifestations. The further loss of fat soluble Vitamins A and D may seriously influence osseous metabolism in the young. Complications associated with the deficiency of Vitamins K and B complex, such as hemorrhage and pellagra respectively, may occur. The combined picture is one of malnutrition, anemia, and exhaustion.

In the diagnosis, steatorrhea is the principal feature

which should be determined by quantitative studies of fecal fat and its partition. Further characteristics are a flat sugar curve, anemia, hypocalcemia, hypoproteinemia, low prothrombin levels and indicanuria. The roentgenologic signs are an ironing out of the valvulae conniventes, occlusive spasm, dilatation and redundancy of the colon, bone changes, and in some instances a poor visualization of the gall bladder with oral dye administration. Therapeutic principles include control of the diarrhea by dietetic measures, replacement of vitamin and calcium losses, restoration of blood, and the administration of bile where needed.—Michael W. Shutkin

HIRSCHBERG, N. AND FANTUS, B. *Mode of Action of Bran* *Rev Gastro-Enterol*, 9 370, Sept., Oct., 1942

The laxative action of bran is usually characterized by large soft stools. In their search for an explanation for the bulk-forming properties of bran they formulated an hypothesis that microorganisms present in the intestinal tract cause a disintegration of certain fractions of bran which results in soft bulky stools containing emulsified gas. The present study involves the relationship of bacteria to the laxative action of bran or the fibrous residues obtained from bran by chemical methods. The experiment was divided into two parts. In part I, a method was used to estimate the amount of bran or bran crude fiber utilized in vitro by stool bacteria of observed individuals. The results of these in vitro studies revealed that both aerobes and anaerobes found normally in stools are capable of disintegrating bran and bran crude fiber and of producing and utilizing the products of disintegration. In part II, an in vitro experiment was planned to determine whether bran ingestion causes some qualitative or quantitative change in the kind or number, or in the potential capacity of intestinal bacteria to produce this emulsified gas. Results showed that all stools tested contained aerobes and anaerobes, capable of producing gas from bran. Further more, bran has no apparent influence on the kind or number of gas-producing bacteria nor does it influence the stool bacteria to produce gas.—Michael W. Shutkin

SCHENKEN, J. R. AND MOSS, E. S. *Enterobius Vermicularis in the Appendix* *Am J Clin Path*, 12 509, Oct., 1942

A study of 1000 consecutively removed appendices from the surgical services of the Charity Hospital of Louisiana at New Orleans was made to determine the incidence of appendiceal infection by *Enterobius Vermicularis* in that locality by means of a standardized method of procedure. The method used first was to emulsify the entire contents of the appendix in water in a test tube and centrifuge it for one minute, after which the supernatant fluid was discarded and the entire sediment examined microscopically. Six hundred cases were examined in this way. Four hundred subsequent cases were examined in like manner with the exception that repeated centrifugation was carried out until the supernatant liquid was clear—and the clean sediment then examined. The results obtained were briefly as follows: Twenty-three and three-tenths per cent of all of the appendices were infected with *E. Vermicularis*. Forty-two and one-tenth per cent of the appendices from white females, and 38.3 per cent of the appendices from white males were infected in the second group. Ten and one-tenth per cent of the appendices from negro females and 12.8 per cent of the appendices from negro males were infected in the second group.

The findings in group 2 were considered more accurate than those of group 1 because of the improved technic used. Great variation in the incidence of such appendiceal infection is found in both American and European published reports. Still's original study in 1899 gave an incidence of less than one per cent whereas Harris and

Digestion and the Nervous System*

A Review of the Literature

By

J. E. THOMAS, M.D.†

PHILADELPHIA PENNSYLVANIA

THE influence of the nervous system on the organs of digestion has always been an important consideration in medical practice, recently it has become a major problem in military medicine. Most physicians have noted the frequent occurrence of digestive disorders associated with conditions which primarily affect the nervous system. Since most of these difficulties arise from emotional disturbances, anxiety or pain, they tend to be aggravated in times like the present when large sections of the population are subjected to unprecedented emotional stresses. A. G. Nicholls (1) in an editorial in the Canadian Medical Association Journal states that "Of late it has become increasingly evident that disorders of the alimentary tract, peptic ulcer in particular, must be regarded as the major medical disability of war time." Sir Arthur Huist (2) in his book on medical diseases of the war observes that "Dyspepsia is the largest single type of disease in the British Army and from several points of view the most important medical problem of the war." The evident increase in digestive disturbances in war time could be due to a variety of causes but it is apparent that an appreciable proportion of them is neurogenic. Colonel Kantor (3) found that more than one-third of the cases which he saw in his gastro-intestinal service during the first world war were suffering from what he called "digestive neuroses." He quotes Colonel Faust to the effect that between 18 and 20 per cent of all patients admitted to the gastro-intestinal and metabolic sections of the Fitzsimmons General Hospital in Denver during the present emergency eventually turn out to have neuroses of some type.

In order to make conveniently available our present knowledge of the mechanism that may be involved in these phenomena, it has seemed worth while to undertake a review of the literature. To this will be added some hitherto unpublished observations made in the Jefferson Physiological Laboratory.

Since the influence of the nervous system on the digestive organs must be transmitted through the peripheral autonomic nerves, it will be convenient first to consider what is known of the action of such nerves on the organs of digestion.

1 EXTRINSIC INNERVATION OF THE STOMACH

The stomach receives its parasympathetic nerve

supply by way of the vagus nerves. Some of the functions of this innervation may be ascertained by observing the effects of vagotomy. Gastric motility in vagotomized animals has been studied by a number of investigators including Cannon (4), Auer (5) and Carlson (6), and more recently Meek and Herrin (7). All investigators are agreed that the immediate effect of vagotomy is a pronounced loss of tonus and motility in the fasting stomach. Food given subsequently does not induce peristalsis. However, according to Cannon (8) if a cat is fed previous to operation peristalsis may continue following vagotomy until the food already present in the stomach has been disposed of. D. C. Cidei and I have tried to repeat this observation on dogs, without success. In two animals one vagus nerve was severed and the other exposed and a strip of cellophane slipped under it so that it could be brought into view at will without seriously disturbing the animal. The dogs were then fed and their gastric motility recorded by means of water manometers on smoked paper. When vigorous peristalsis had begun we brought the remaining vagus into view and divided it with a quick snip of a pair of scissors. The peristaltic activity in the stomach ceased at once and although the animals were observed for hours following, it did not return during that period of observation (Cidei and Thomas, unpublished).

After several days following vagotomy there is a gradual return of tonus in the stomach and ultimately something approaching normal motility may again be recorded. There is considerable difference of opinion with regard to the return of normal gastric emptying. Details of this controversy are given in a review by McSwiney (9). Meek and Herrin (7) believe that the variations in results reported by different investigators are caused by differences in the type of food used as a test meal. In their animals, some of which lived for five months, there was a permanent delay in emptying solid food from the stomach. Liquids, however, left the stomach in normal time. We have had occasion to observe a number of vagotomized animals and our observations are in agreement with those of Meek and Herrin.

The effect on the stomach of stimulating the peripheral parts of the severed vagus nerves has been studied extensively. Only the more significant observations need be mentioned. Most observers agree that the predominant effect of vagal stimulation on all parts of the stomach is to increase the tonus and the activity of the smooth muscle. A considerable number,

*Condensed from the annual A.O.A. lecture delivered at St. Louis University School of Medicine November 23, 1942.
†Jefferson Medical College Philadelphia Pa.
Submitted February 27, 1943.

however, beginning with Openchowski (10) have observed on occasion the opposite effect, that is, relaxation both of the sphincters and of the smooth muscle in the body of the stomach. Thomas and Wheelon (11) studied the action of the vagus on the pyloric antrum, pyloric sphincter and first part of the duodenum. In their experiments stimulation of either vagus nerve generally increased the activity of the muscle in this region, but in a few experiments relaxation occurred, especially when very weak electrical stimuli were applied. Langley (12) had previously observed relaxation of the cardiac sphincter and the lower end of the esophagus in animals in which the vagus nerves were stimulated following administration of moderate doses of atropine. Carlson (13) verified these results and showed that excitatory responses were obtained most frequently when the muscle was in a state of contraction or possessed a high degree of tonus, whereas inhibitory effects were observed when the muscle initially was relaxed. This relationship between initial tonus and the response to nerve stimulation has been confirmed by a number of investigators and is the accepted explanation at the present time for the occurrence of so-called reversal effects whether from stimulation of the parasympathetic or sympathetic nerves.

Section of the splanchnic nerves has less effect on gastric motility than does division of the vagi. However, an increase in tonus and in motility of the stomach has been reported by most investigators. In a recent study by Barron (14) similar results were obtained in human subjects. The effects on the stomach of stimulation of the peripheral parts of the divided splanchnic nerves are varied and complex. Numerous studies have been made, among the more recent are those of Carlson, Boyd and Percy (13), Thomas and Wheelon (11), McCrea and McSwiney (15), and Brown, McSwiney and Wadge (16). Nearly all investigators agree that the gastric muscle may be either stimulated to increased activity or inhibited through the splanchnic nerves. Nearly all are agreed also that motor effects occur more frequently in stomachs in which the tonus is low and inhibitory effects when the tonus is high. It is probably true that in acute experiments the tonus of the stomach is practically always abnormally low, hence the frequent occurrence of motor effects during sympathetic stimulation observed in such experiments is, in a quantitative sense, something of an artifact.

2 EXTRINSIC INNERVATION OF THE SMALL INTESTINE

In the small intestine parasympathetic denervation through cutting the vagus nerves has apparently only minor effects on the activity of the smooth muscle. The subject has not been sufficiently investigated but in the animals that we have studied even casual observation was sufficient to show that intestinal stasis did not occur. Cannon (4) observed a slight delay in the passage of certain foods through the intestine following vagotomy but peristalsis and segmenting contractions were still present.

Bavliiss and Starling (17) observed that stimulation of the peripheral vagus usually caused increased activity of the muscle of the small intestine. Occasionally the motor effect was preceded by a brief period of inhibition but in no case did they observe prolonged inhibitory effects in the small intestine.

There is little information regarding the effects of sympathetic denervation on the motility of the small intestine. Cannon (4) has reported an increase in the rate of passage of food through the intestine following section of the splanchnic nerves.

It is universally agreed that stimulation of the sympathetic nerves that supply the small intestine results in loss of tone and cessation of motility in a vast majority of instances. Exceptions occur, however, even here, e.g. in the experiments of Thomas and Wheelon already mentioned the first part of the duodenum responded with contraction to sympathetic stimulation just as frequently as did the adjacent parts of the stomach. In experiments on excised nerve muscle preparations of the intestine I (18) have occasionally observed secondary contraction following a brief primary inhibition when the mesenteric nerves were stimulated electrically. This result was seen after degenerative section of the vagus nerves which should leave only postganglionic sympathetic fibers in mesenteric nerves. However, for the most part the effects were inhibitory.

3 EXTRINSIC INNERVATION OF THE LARGE INTESTINE

The large intestine receives its parasympathetic innervation largely via the pelvic nerves and to only a negligible extent through the vagi. The effect of cutting the parasympathetic nerves only has not been studied, so far as I can learn, but complete denervation was accomplished by Elliott and Barclay-Smith (19) who destroyed the spinal cord in a number of animals of various species. Following this procedure they observed a marked decrease in motor activity of the large intestine characterized by retention of contents and accumulation of fecal masses in the distal colon. Since these phenomena do not result from sympathetic denervation, they were probably due to loss of the parasympathetic nerve supply.

The effect on the large intestine of stimulating the parasympathetic nerves in dogs and rabbits was studied by Bayliss and Starling (20) who concluded that these nerves augment the activity of both the circular and longitudinal muscle. Their results confirmed those obtained by Langley and Anderson (21) in rabbits and cats. The latter authors had also made the observation that the parasympathetics cause relaxation of the internal anal sphincter. Recently Wells, Mercer, Gray and Ivy (24) have corroborated these findings in dogs, pigs and monkeys.

I know of no recorded observations of the permanent effects of sympathetic denervation of the large bowel in normal experimental animals but in my own experience (Thomas, unpublished) removal of the in-

femoral mesenteric ganglia caused a persistent diarrhea in dogs. In humans suffering from congenital megacolon, sympathetic denervation results in recovery of normal tonus and contraction of the dilated colon.

Electrical stimulation of the sympathetic nerves supplying the large intestine has given various results in the hands of different investigators. Bayliss and Starling (20) saw only relaxation of both circular and longitudinal muscle coats during sympathetic stimulation, whereas Langley and Anderson (21) reported both motor and inhibitory effects accompanied by strong contraction of the internal anal sphincter, especially in cats. Elliott and Barclay-Smith (19) agreed with Bayliss and Starling, while Carlson's (22) results are in accord with those of Langley and Anderson. Learmonth and Markowitz (23) found that stimulating the lumbar sympathetic trunks or the hypogastric nerves caused only relaxation of the muscle in the wall of the large bowel but caused strong contraction of the internal anal sphincter. Within the past year Wells, Mercer, Gray and Ivy (24) have reported that they were able to observe only motor effects on stimulation of the hypogastric nerves to the large intestine in dogs.

The key to these apparently inconsistent data is furnished by Carlson's study (22). He found that in the large intestine, as in the stomach, stimulation of the sympathetic nerves caused contraction when the tonus of the muscle was low and relaxation at other times. The results of nerve section already mentioned indicate that the predominant action of the sympathetic innervation to the large bowel is inhibitory in the normal animal.

4 EXTRINSIC REFLEXES

Reflexes affecting gastro-intestinal organs due to stimuli conducted through the peripheral autonomic nerves have not been investigated as extensively as their probable importance deserves. A few, however, are well known and may be mentioned as suggesting the possibilities in this field. Cannon and Lieb (25) observed relaxation of the gastric muscle associated with the act of swallowing. This they called the receptive relaxation of the stomach. This inhibitory effect disappeared when the vagi were severed. Thomas, Crider and Mogan (26) found that a variety of stimuli when applied to the small intestine resulted in loss of tonus and diminished peristaltic activity in the digesting stomach. We named this phenomenon the enterogastric reflex. This reflex also disappears when the vagus nerves are severed. It is not affected by division of the splanchnic nerves. We are thus confronted with the surprising fact that two well-known reflexes causing inhibition of gastric motility utilize the vagus nerves as a peripheral path.

Stimulation of the oral, gastric, or intestinal mucosa inhibits gastric hunger contractions. Carlson (27) found that the reflexes from the gastric and intestinal mucosa could be conducted through either the vagi, the splanchnics, or the local nerve plexus. The defecation reflex should also be mentioned. Judging from

the behavior of the smooth muscle involved, this is mainly a parasympathetic reflex.

Reflexes affecting the gastro-intestinal muscle by way of the sympathetic innervation are for the most part initiated by noxious stimuli. The demonstration of the effects of such stimuli on the gastro-intestinal tract we owe chiefly to Cannon and Murphy (28), who found that under anesthesia various manipulations which would cause pain to unanesthetized animals caused pronounced inhibition of the stomach and intestines. Such inhibition, however, was not obtained if the splanchnic nerves had previously been divided. An exception to this was found in cases in which the harmful stimuli were applied directly to portions of the gastro-intestinal tract. In such instances inhibition occurred even in the absence of extrinsic innervation. The authors expressed the belief that in these instances the inhibitory effects were mediated by the intrinsic plexuses in the walls of the stomach and intestine.

Any discussion of reflexes affecting the gastro-intestinal tract would be incomplete without a consideration of the functioning of local reflex mechanisms resident in the organs themselves or in adjacent ganglia. Bayliss and Starling (17) in their extensive study of the innervation of the small intestine discovered what they termed "the law of the intestine." According to their observations, an adequate stimulus of any sort applied to the intestine caused contraction of the muscle at and above the stimulated point and relaxation below. Normally this contraction preceded by relaxation travels along the intestine, constituting a peristaltic movement. They attributed this response to stimuli conducted through the myenteric plexus. Cannon (29) later studied the same phenomenon and arrived at much the same conclusions. He suggested that the reaction be called "the myenteric reflex" and this is its common name at present. Most physiologists have accepted the views of Bayliss and Starling and of Cannon and with few exceptions regard the myenteric plexus as a peripheral reflex mechanism capable of mediating important reflexes quite independently of the central nervous system. This mechanism is considered to be in part responsible for the co-ordination of gastro-intestinal activity. Anatomists, on the other hand, were slow to accept this point of view largely because of the absence of histological evidence for the occurrence of reflex arcs in peripheral ganglia. This deficiency in anatomical knowledge was remedied by the observations of Kuntz (30), who demonstrated the occurrence of synaptic junctions between the axons of cells in the myenteric plexus and the dendrites of adjacent cells.

More recently evidence is accumulating that peripheral reflex arcs occur in sympathetic ganglia outside the myenteric plexus. Kuntz and Van Buskirk (31) have found that certain reflexes affecting bile flow and the motility of the small intestine may be obtained under conditions that effectively exclude participation of either the long reflex paths through the central

nervous system or the enteric plexuses. The most probable paths, they think, for these reflexes are reflex arcs with their centers in the celiac ganglia. About the same time Warkentin and Ivy (32) reported a study of enterogastric regurgitation (the regurgitation of bile into the stomach when acid is placed in the intestine) in which their evidence, admittedly incomplete, suggests that this activity may be mediated by reflexes through the celiac plexus in the absence of the extrinsic innervation.

5 INNERVATION OF THE DIGESTIVE GLANDS

Because of the great emphasis that has been placed in recent years on hormonal control, we are apt to forget that the nervous system also plays an important part in regulating the activity of various digestive glands. As is well known, the salivary glands are entirely dependent upon their autonomic nerve supply for their normal functioning. The regulation of the gastric glands through the vagus nerves also plays an important part in normal digestion. The relation of the vagi to gastric secretion was first demonstrated by Pavlov and Simanowskaja (33) in 1895. They showed not only that electrical stimulation of these nerves in experimental animals caused secretion of acid and pepsin by the gastric glands but also that the immediate response of the gastric glands to a meal disappeared after the vagus nerves had been cut. Although gastric secretion occurs following vagotomy, it does not appear until after a longer than normal latent period and the volume and digestive power of the secretion are far less than in normal animals.

Stimulation of the splanchnic nerves causes secretion of mucus only in the stomach according to Baxter (34) but Volborth and Kudryavzeff (35) were able to demonstrate some slight effect on the gastric glands proper, resulting in the secretion of a small amount of typical gastric juice.

There is good evidence also for the belief that pancreatic secretion, particularly the production of enzymes, is under nervous control. Pavlov (36) demonstrated secretory as well as inhibitory fibers for the pancreas in the vagus nerves. Stimulation of the vagi produces pancreatic secretion which is especially rich in enzymes. The splanchnic nerves also have been found to contain secretory fibers for the pancreas in some animals. In the rabbit splanchnic stimulation increases both the volume and the enzyme content of the pancreatic secretion (Baxter, 37) but Harper and Vass (38) found that in the cat the sympathetic nerves caused inhibition, especially of enzyme secretion. Kudrewetzky (39) and Babkin, Hebb and Sergeeva (40) found secretory fibers for the pancreas in the splanchnic nerves of dogs.

The utility of the secretory nerves to the pancreas has been a matter of some mystery. Since the demonstration by Bayliss and Starling (41) of the existence of a secretory hormone for the pancreas, the humoral mechanism has been regarded by many as adequate to explain the activity of the pancreas during digestion.

However, it has long been known that the total concentration of enzymes in pancreatic juice differs according to the different types of food undergoing digestion. Since secretin produces a secretion of approximately constant concentration, the variations in composition alone are sufficient evidence that some other mechanism than secretin normally contributes to the regulation of pancreatic activity.

Reflexes affecting gastro-intestinal secretions have been studied, particularly in Pavlov's laboratory. The so-called psychic secretion of saliva and gastric juice in response to sight, smell or taste of food is now a matter of common knowledge. These responses all disappear when the parasympathetic nerves supplying the various glands have been cut. They are therefore, parasympathetic reflexes.

Whether noxious stimuli which primarily affect the sympathetic division of the autonomic nervous system affect gastro-intestinal secretions as they do motility appears not to have been sufficiently investigated. However, Pavlov and others have found that "psychic" secretion of saliva and gastric juice is inhibited during periods of excitement (see Cannon, 42). Dryness of the mouth, suggesting inhibition of salivary secretion, is a common symptom of fright. We know that the digestive secretions are often inhibited by anesthesia and operative trauma in acute experiments as is the motility. In conscious animals we have observed cessation of secretion of acid from a Pavlov pouch of the stomach during periods of nausea and vomiting. Further studies along this line are needed.

6 CENTRAL MECHANISMS

The nerve fibers found in the preganglionic autonomic nerves are the axons of nerve cells situated in the spinal cord or in the medulla. It is known, however, that many of the impulses which activate these neurons arise at a higher level in the central nervous system. The recent work of Cushing (43) and of Ranson and his associates (44, 45) and the older work of Karplus and Kreidl (see Karplus, 1928) (46) and of Beatty, Brau and Long (47) have proved beyond reasonable doubt that centers for autonomic reflexes are located in the hypothalamus. Electrical stimulation of this structure in anesthetized animals causes various visceral changes, including gastro-intestinal inhibition. In unanesthetized animals it causes all the external manifestations of strong emotion. Recent evidence (45) indicates that some of the nuclei in the hypothalamic area send impulses over the parasympathetics causing increased gastro-intestinal activity.

The afferent paths to the hypothalamus are such that it may receive impulses directly from peripheral sense organs, or indirectly by way of the thalamus or the cerebral cortex. The thalamus is believed to contain the centers in which the painful or pleasurable qualities of sensations are perceived. Its connections with the hypothalamus provides a mechanism through which affective stimuli may reach the hypothalamic nuclei, from these they may be transmitted to the

viscera by means of the autonomic nerves. In this way stimuli which cause disagreeable or pleasurable emotions eventually affect the internal organs, including the organs of digestion. For these reasons it is not surprising to find that pain, fear, anger, resentment, or worry are often associated with gastro-intestinal disturbances.

Some of the implications of these facts have been admirably set forth by Professor Cannon (42). Cannon's emphasis on the "sympathetico-adrenal system," however, has led to the belief that visceral emotional responses are mediated for the most part through the sympathetic division of the autonomic system. This may be true for certain types of reactions but emotions differ among themselves in their external manifestations and there is no reason to assume that their visceral expressions will always be identical or will always involve the same nervous pathways. In the case of the organs of digestion at any rate there is good reason to believe that certain types of emotional reactions are associated with stimulation of the parasympathetic nerves. Attention has been called to this fact by Todd (48) who reported that "hyperactivity of the stomach is always present in the anxiety complex in patients consciously or subconsciously nervous but not afraid." The recent interesting study by Wolf and Wolff (49) of a patient who has a permanent gastric fistula, provides strong

support for Todd's views. Wolf and Wolff were able to differentiate between the response of their patient's stomach to stimuli causing fear or anger and those which resulted in the more chronic state of anxiety and resentment. Whereas the former caused blanching of the mucosa and inhibition of secretion and motility, the latter caused increased secretion and increased motility with flushing of the mucosa, all of such degrees as to establish a condition which they thought was favorable to ulceration.

Should these observations prove to be applicable generally, it would be difficult to overemphasize their importance. The type of reaction which is associated with the peripheral manifestations of sympathetic stimulation is generally transient. The very intensity of such emotions prevents their being long sustained. On the other hand, feelings of anxiety and resentment may continue for weeks or months and so may give rise to chronic anatomical changes in the organs affected. Perhaps peptic ulcer is only one of many such manifestations.

Dr. Ivy has quoted Josh Billings to the effect that a reliable set of bowels is worth more to a man than any quantity of brains. What Josh Billings apparently didn't know is that the quality if not the quantity of the brains has a lot to do with the reliability of the bowels.

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Gall Bladder Visualization With B (3,5 di-iodo-4-hydroxyphenyl) α Phenyl Propionic Acid (Priodax*)

By

I H EINSEL, M.D

and

T H EINSEL, M.D

CLEVELAND OHIO

THE intravenous injection of tetra-brom-phenolphthalein (1) or the sodium salt of tetra-iodo-phenolphthalein as suggested by Graham, Cole and Copher (2) or the oral administration of the latter compound by Menees, T O and Robinson, H C (4), has for many years been the method of choice for roentgenologic examination of the gall bladder. Several reports have recently appeared (4-10) indicating that distinct advantages may be associated with the use of β (3,5 di-iodo-4-hydroxyphenyl) α phenol propionic acid. In Germany, this compound is designated as Biliselektan, but the name Priodax is employed in this country. Evidence has been presented indicating that the oral administration of this compound results in gall bladder visualization equal to or superior to that obtained by other methods. Moreover, Biliselektan is claimed to be almost entirely devoid of irritation to the digestive tract, thus one of the most objectionable features of previous methods is avoided.

In the present investigation, preliminary studies with doses ranging between 2 and 5 gm permitted the conclusion that a dose of 3 gm of Priodax was almost universally satisfactory. In many cases, a larger dose increased the density of the gall bladder shadow, but the 3 gm dose was adequate to produce cholecystograph plates which could readily be interpreted. Thus, the following routine was followed throughout the investigation. The meal of the evening preceding the examination consisted of fruit, vegetable, tea and toast, fats were avoided. One hour later 3 gm of Priodax, thoroughly stirred into a cup of tea, was taken. Subsequently, fluids in moderation were permitted, but the ingestion of food was avoided until after the examination made at 9 00 o'clock the following morning. Immediately after the first X-ray plate was taken, the patient was given a glass of equal parts of milk and cream and the yolk of one egg. The

second X-ray plate was made two hours following the first.

In 50 unselected cases (19 male and 31 female) appearing consecutively for cholecystographic examination, the gall bladders of 42 visualized and emptied satisfactorily, emptied 60% in 2 hours. The normal and pathological gall bladder had the same characteristics observed with visualizing agents previously available and yielded the usual information respecting the anatomy and functional activity of the gall bladder, except the emptying process was more gradual. In our experience, Priodax distinguished the normal from the pathological gall bladder as satisfactorily as any contrast material now commonly in use.

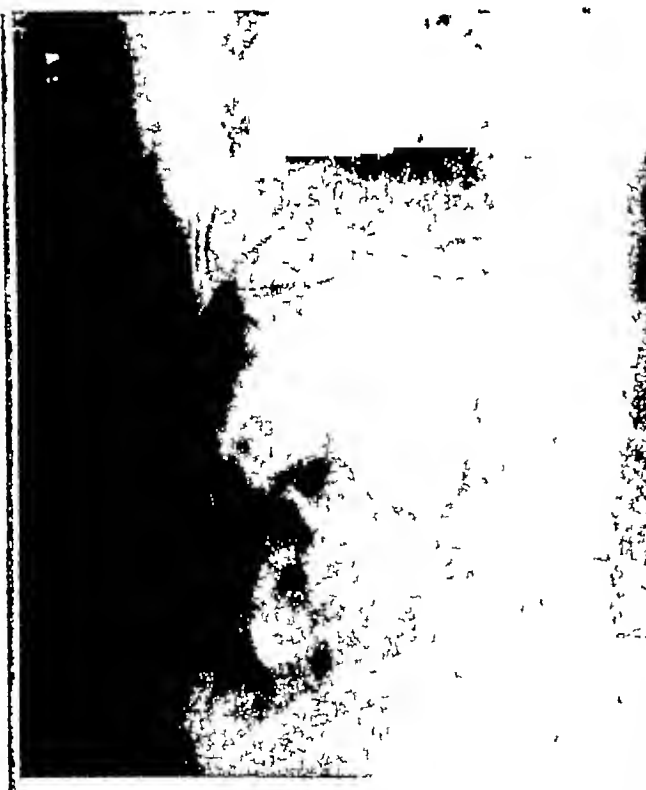
Gall stones were present in 6 cases showing good visualization, but a prolonged emptying time. Two cases with stones failed to visualize but this non-visualization could not be ascribed to the Priodax. Failure of visualization in one of these cases was explained by a complete plugging of the cystic duct encountered subsequently at operation. Two cases showing normal visualization with Priodax had previously failed to visualize with sodium tetra-iodo-phenolphthalein.

The Priodax produced no obvious symptoms except in one patient who reported a mild burning sensation in the "stomach." Doses of Priodax exceeding those required for cholecystography can produce gastro-intestinal irritation, for Dr Walter Modell (personal communication) observed anorexia, nausea and vomiting in cats receiving large doses. This irritation probably results from the local action of the drug in the digestive tract for the gastro-intestinal symptoms were not observed from large doses of the compound administered intravenously.

SUMMARY

Observation made in 50 routine cases of cholecystography confirmed the report that a single 3 gm dose,

*The Priodax used in this investigation was supplied by the Schering Corp. Bloomfield, N. J.
Submitted February 18 1948.



Figs 1 and 2 As shown in Fig 1 and also in Fig 2 (after the administration of fats), the typical gall bladder visualization obtained with 3 gm of Priodax was sufficiently dense to satisfactorily outline the gall bladder



Fig 3 The fact is equally important that in cases of cholelithiasis the Priodax shadow was light enough to provide a good contrast with the gall stones. This is shown in Fig 3. Too dense a shadow from the contrast material may lead to diagnostic errors by masking gall stones, particularly those of the millet seed type



Fig 4 The contrast between the shadow produced by the drug and by stones is illustrated in Fig 4, two hours after the drug had been largely emptied from the gall bladder by a fat meal

of Priodax given orally by a simple technic produced gall bladder visualization equal to or superior to that usually obtained from other contrast materials

Freedom from nausea, vomiting, diarrhea or other indication of gastro-intestinal irritation was an outstanding feature of these examinations

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Studies on the Influence of Various Substances on the Colon: I. Phenolphthalein and Other Laxatives*

By

FREDERICK STEIGMANN, M S, M D, OSKAR WOZASEK, M D

and

JOSEPHINE M DYNIEWICZ, Ph C

CHICAGO ILLINOIS

THE uncertain etiology of colitis has prompted much conjecture as to the probable causative factors. The frequent use of cathartics is considered by some as one of the causes of this affection (1). Certain laxatives, probably because of their frequent use, are especially singled out as responsible for the occurrence of colitis. In the published literature, most of the opinions concerning the causation of colitis by cathartics are based on impressions obtained from the patient's personal history of his illness and from rather superficial clinical observation, without the aid of thoroughgoing laboratory studies to elicit the facts, and without control investigations to prove or disprove any impressions gathered.

Colitis is a term frequently used, doubtless too loosely, for denoting any condition in which there is evidence of some vaguely defined disturbance in the abdomen. Patients are all too freely labeled as suffering from colitis when they complain of any of the multitude of gastro-intestinal symptoms, without revealing any organic changes by X-ray and routine laboratory tests. Accuracy would hardly permit the

use of the designation colitis except in conditions of a truly inflammatory nature, such as ulceration of the colon due to amoebic or bacillary infection and other causes. Aside from these factors, there are hardly any criteria that permit the assumption of the presence of colitis. Too often, the term colitis is being applied to conditions that are not accompanied by inflammation of the colon, and the diagnosis is based simply on the existence of certain symptoms in the gastro-intestinal tract which but remotely justify this diagnostic designation.

With our present knowledge of the condition, colitis may only be established by the findings revealed by proctosigmoidoscopy and by the constituents of the stool. The fecal constituents aid in the classification of the types of colitis, they help to establish whether they are of amoebic, or bacillary origin, and whether they are of ulcerative or inflammatory type.

In our search for a method by which the existence of colitis could be determined, or its presence ruled out, in patients who do not show evidence of an inflammatory or ulcerative process, we have examined a large number of specimens of stools obtained from normal individuals as well as from patients with and without gastric disturbances, to establish as definitely as possible the constituents of normal and abnormal

*From the Departments of Internal Medicine and Pharmacology and Therapeutics, University of Illinois College of Medicine and the Department of Therapeutics and Gastro-Intestinal Clinic of the Cook County Hospital, Chicago, Illinois.
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TABLE I
Preliminary period (172 cases)

No. of Cases	No. Days of Observation	Daily Average of				Percentage of Cases Having		
		Stool Wt in Gms	No. of Stools	Percentage of Moisture	Chemie Mucus in cc Per Gm of Stool	Chemie Mucus More Than 0.1 cc	Strings	Protein
50	3	100	1.03	74.3	0.67	20	20	8
32	3	95	1.06	73.7	0.65	34.4	18.75	0
30	3	111	.99	75.0	0.61	16.7	33.33	3.33
30	3	89	1.06	72.4	0.62	13.33	13.33	0
30	3	99	1.01	73.7	0.65	23.33	26.66	6.66
Summary 172	3	99	1.04	73.9	0.65	21.37	22.14	4.1

stools. The results of this study (2) clearly indicate that there are wide variations in the constituents of stools and confirm the fact that frequently diagnosis of colitis is made clinically when there are no signs of colon irritation to support such conclusion, as judged by repeated stool examinations. Briefly stated, it was found that normally the stool contains not more than 0.1 cc of mucus in every gram, and no mucous strings or protein. Utilizing our newly acquired information concerning the constituents of the stools that are usually indicative of an inflammatory condition (colitis) or of irritation, we have undertaken an investigation of the effect of various laxatives on the colon by comparing the fecal constituents before and after the ingestion of substances that produce a laxative effect.

METHOD AND PROCEDURE

Normal individuals, both men and women, were used as subjects. They were classified as normal inasmuch as they were not conscious of any symptoms and had

not exhibited any signs that may have indicated a deviation from the normal. During the period of investigation they continued at their usual occupations and subsisted on their customary diet. Each subject collected 24-hour specimens of stool for 3 days before any medication was given. This was termed the *preliminary period*. After this, a laxative was given, and the stools were again collected for three days. This was termed the *examination period*. During the final, or *after-examination period*, the stools were again collected for 2 or 3 days. As a method of control, these subjects received during one examination period, a large quantity of fruits only as part of their diet. No laxative substance was used during this period. All stools were examined chemically for mucus, protein, and urobilinogen, and microscopically for mucus, mucous strings, and cells.

Tests were made with various laxatives: phenolphthalein, USP and yellow, in various doses, with

TABLE II
0.06 Gm white phenolphthalein period (122 cases)

	No. of Cases	No. Days of Observation	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
			Stool Wt in Gms	No. of Stools	Percentage of Moisture	Chemie Mucus in cc Per Gm of Stool	Chemie Mucus More Than 0.1 cc	Strings	Protein	Cramps	Flatulence	Laxative Effect
(a) Preliminary	30	3	111	.99	75.0	0.001	10.7	33.33	3.33			
0.06 Gm white Phenolphthalein		2	132	1.13	77.6	0.061	6.60	13.33	0	13.33	46.6	40
Post		2	101	.93	74.0	0.000	16.7	10.7	3.33			
(b) Preliminary	30	3	89	1.06	72.4	0.052	13.33	13.33	0			
0.06 Gm white Phenolphthalein		2	116	1.13	70.5	0.067	23.33	3.33	10.0	23.33	26.66	50
Post		2	109	1.02	74.7	0.065	16.66	6.66	3.33			
(c) Preliminary	30	3	99	1.01	73.7	0.065	23.33	26.66	6.66			
0.06 Gm white Phenolphthalein		2	128	1.19	75.6	0.067	30.0	16.66	6.66	13.33	20	26.7
Post		2	110	1.03	75.0	0.057	16.66	33.33	10.0			
(d) Preliminary	32	3	95	1.06	73.7	0.068	34.4	18.75	0			
0.06 Gm white Phenolphthalein		2	150	1.33	78.6	0.065	21.87	21.87	3.13	28.12	37.5	50.4
Post		2	89	.93	75.2	0.059	12.50	18.75	0			
SUMMARY												
(e) Summary—Pre.	122	3	90	1.03	73.7	0.064	21.94	23.02	2.5			
Phenolphthalein		2	132	1.20	77.1	0.065	20.47	13.8	4.05	10.53	32.7	44
Post		2	104	0.92	75.0	0.052	15.7	18.86	4.17			

TABLE III
0.012 Gm white phenolphthalein period (115 cases)

	No. of Cases	No. Days of Observation	Daily Average of		Chemie Mucus in cc. per Gm. of Stool	Percentage of Cases Having			Subjective Symptoms		
			Stool Wt. in Gms	No. of Stools		Chemie Mucus More Than 0.1 cc.	Strings	Protein	Cramps	Flatulence	Laxative Effect
(a) Preliminary	30	3	112	0.9	72.9	0.049	13.33	10	0		
0.120 Gm white Phenolphthalein		2	186	1.18	80.3	0.057	10	16.66	0	16.66	40.0
Post		2	105	0.05	75.8	0.055	6.66	13.33	0		66.66
(b) Preliminary	30	3	91	1.09	73.6	0.061	13.33	6.66	3.33		
0.120 Gm white Phenolphthalein		2	139	1.15	80.0	0.030	20.0	10.0	0	33.33	36.66
Post		2	87	88	75.1	0.061	13.33	6.66	3.33		56.66
(c) Preliminary	30	3	98	1.01	72.7	0.068	26.66	30.0	3.33		
0.120 Gm white Phenolphthalein		2	157	1.33	77.2	0.068	16.66	25.66	3.33	36.66	48.33
Post		2	95	1.10	72.8	0.081	30.0	30.0	3.33		66.66
(d) Preliminary	25	3	89	1.03	73.9	0.066	32.0	20.0	0		
0.120 Gm white Phenolphthalein		2	163	1.44	70.7	0.058	4.0	8.0	0	36.0	32.0
Post		2	90	1.09	76.2	0.066	12.0	20.0	0		88.0
SUMMARY											
(e) Preliminary	115	3	97	1.01	73.3	0.062	21.33	16.67	1.67		
Phenolphthalein		2	161	1.23	79.3	0.061	12.67	16.33	0.83	30.66	38.0
Post		2	97	1.01	75.0	0.066	16.5	17.5	1.67		69.5

aromatic fluidextract of cascara sagrada, magnesium sulfate, bran, kaiaua gum and prostigmin bromide

RESULTS

I Preliminary Period

Altogether, the daily stools of 172 normal individuals were examined for three consecutive days, or a total of 500 specimens. For statistical comparison, the individuals serving as test subjects were divided into one group of 50, one group of 32 and three groups of 30 each. Applying our criteria of normal and abnormal stool constituents, we found that the stool specimens obtained during the preliminary period from these normal subjects contained abnormal constituents in varying percentages.

Increased mucus was found in 20 to 24 per cent of the specimens examined (average 21.37%), mucous strings in 13 to 33 per cent (average 22.14%), and protein in 0 to 8 per cent (average 4.1%) (Table I).

II Tests with Phenolphthalein

During the phenolphthalein period, the subjects received at weekly intervals two different doses and different types of phenolphthalein. Thus, some received 0.06 Gm of white (USP) phenolphthalein followed by 0.12 Gm white (USP) and then by 0.06 Gm yellow phenolphthalein while others received first the yellow and then the white (USP) phenolphthalein. Altogether the phenolphthalein period, including the preliminary tests lasted four weeks. For statistical comparison the subjects receiving the phenolphthalein were divided into four groups of about 30 each.

One hundred twenty-two individuals received 0.06 Gm of white (USP) phenolphthalein as a test dose. Tables IIa, IIb, IIc and IId show the percentage of subjects in each group having mucus above 0.1 cc./Gm.

of stool, or having mucous strings or proteins in the preliminary period and test periods respectively. Table IIe summarizes the findings in the entire group. It demonstrates that in this group of 122 normal individuals, mucus in excess of 0.1 cc./Gm of stool was present in 21.94%, mucous strings in 23% and protein in 2.5%. During the 0.06 Gm phenolphthalein test period, the above percentages changed to 20.47%, 13.8% and 4.95% respectively. During the post-phenolphthalein period, mucus in excess of 0.1 cc./Gm was found in 15.7%, mucous strings in 18.86% and protein in 4.17%.

One hundred fifteen normal subjects, most of whom had received, one week prior, 0.06 Gm of phenolphthalein received 0.12 Gm of white (USP) phenolphthalein as a test dose. They were also divided into four groups. Tables IIIa, IIIb, IIIc and IIId show the percentage of subjects in each group having mucus above 0.1 cc./Gm of stool, or having mucous strings or proteins in the preliminary period and test periods respectively. Table IIIe summarizes the findings in the entire group of 115 individuals. It shows that as a group 21.3% of these subjects had mucus in excess of 0.1 cc./Gm, 16.6% had mucous strings and 1.6% had protein during the preliminary period. During the 0.12 Gm white (USP) phenolphthalein test period the percentages were 12.6, 15.3 and 0.8 respectively. In the post-phenolphthalein period mucus over 0.1 cc./Gm of stool was found in 15.5%, mucous strings in 17.5% and protein in 1.6%.

One hundred fourteen of the subjects tested above received 0.06 Gm of yellow phenolphthalein as a test dose. They, too, were divided into four groups. Tables IVa, IVb, IVc and IVd show the respective percentages of excess mucus, of mucous strings and of pro-

TABLE IV
0.06 Gm yellow phenolphthalein period (114 cases)

	No of Cases	No Days of Observation	Daily Average of			Percentage of Cases Having			Subjective Symptoms			
			Stool Wt in Gms	No of Stools	Percentage of Moisture	Chemle Mucus in cc Per Gm of Stool	Chemle Mucus More Than 0.1 cc	Strings	Protein	Cramps	Flatulence	Laxative Effect
(a) Preliminary	30	3	107	1.00	73.6	0.054	3.33	20	3.33			
0.06 Gm yellow Phenolphthalein		2	170	1.17	80.2	0.056	3.33	16.66	0	16.66	50.0	76.66
Post		2	105	0.97	73.7	0.060	6.66	6.66	0			
(b) Preliminary	30	3	91	1.03	78.2	0.063	13.33	13.33	3.33			
0.06 Gm yellow Phenolphthalein		2	142	1.23	78.0	0.066	23.33	13.33	3.33	43.33	36.66	66.66
Post		2	87	0.91	76.0	0.067	13.33	10.0	3.33			
(c) Preliminary	30	3	103	1.09	73.6	0.066	23.33	23.33	3.33			
0.06 Gm yellow Phenolphthalein		2	167	1.37	79.6	0.065	26.66	13.33	0	53.33	50.0	70.0
Post		2	89	1.18	73.0	0.067	20.0	16.66	6.66			
(d) Preliminary	24	3	86	1.02	73.9	0.066	25.0	20.83	0			
0.06 Gm yellow Phenolphthalein		2	162	1.43	70.1	0.064	16.66	12.50	8.33	87.5	83.33	79.17
Post		2	88	1.05	74.1	0.071	20.17	25.0	0			
SUMMARY												
(e) Preliminary	114	3	97	1.05	73.6	0.062	16.25	10.87	2.5			
Phenolphthalein		2	160	1.3	79.2	0.063	17.5	13.95	2.92	37.7	42.5	73.12
Post		2	92	1.03	74.2	0.066	17.29	14.58	2.5			

tein during the preliminary periods and during the test period of each group. Table IVe summarizes the findings in the entire group during the different periods. It reveals that of these 114 subjects, as a group, 16.2% had mucus in excess of 0.1 cc/Gm of stool, 19.3% had mucous strings and 2.5% had protein during the preliminary period. During the phenolphthalein period, the percentages were 17.5%, 13.9% and 2.9% respectively. During the post-phenolphthalein period, mucus in excess of 0.1 cc/Gm was found in 17.3%, mucous strings in 14.6% and protein in 2.5%.

III Tests with Bran

Fifty normal subjects submitting to these tests, showed in their stools, taken during the preliminary period, mucus in excess of the normal in 20%, mucous strings in 20%, and protein in 8%. During the bran period, mucus was found in 20%, strings in 24%, and protein in 10%. During the period after the taking of bran, there was mucus in 24%, strings in 18%, and protein in 8% (Table V).

IV Test with Karaya Gum

Thirty normal individuals received 20 Gm Mucin-K, a karaya gum preparation, daily for 3 days. During the period before taking the gum, 16.6% had excessive mucus in the stools, 30% had mucous strings, and none had protein. During the period the gum was taken, mucus was found in 13.3%, strings in 60%, protein in none. The after-period revealed mucus in 10%, strings in 30%, and protein in none (Table VI).

V Test with Magnesium Sulfate

There were 31 subjects in this group, and each was given a single dose of 15 Gm of magnesium sulfate. Of this number, during the preliminary period, 19.4% had excessive mucus in the stool, 29% had mucous strings, and none had protein. During the period when magnesium sulfate was administered, increased mucus was found in 12.9%, strings in 22.6%, and protein in none. Three days after the magnesium sulfate was taken, excessive mucus was present in 16%, strings in 22.6%, and protein in 3.2% (Table VII).

TABLE V
Bran period (50 cases)

Periods	No Days of Observation	Daily Average of			Percentage of Cases Having			Subjective Symptoms			
		Stool Wt in Gms	No of Stools	Percentage of Moisture	Chemle Mucus in cc Per Gm of Stool	Chemle Mucus More Than 0.1 cc	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary	3	100	1.08	74.3	0.067	20	20	8			
Bran	4	121	1.13	75.5	0.058	20	24	10	8	12	44
Post—4 days later	3	82	0.92	73.5	0.066	24	18	8			

VI Test with Cascara Sagrada

Thirty normal individuals received one dose of 4 cc aromatic fluidextract cascara sagrada. The results of examination during the preliminary period, were mucus in excess in 19.3%, mucous strings in 25.8%, and protein in none, during the period of cascara medication, mucus was present in 22.5%, strings in 32.2%, and protein in 3.2%, during the post-medication period, mucus was found in 12.9%, strings in 25.8%, and protein in none (Table VIII).

VII—Test with High Fruit Diet

A high supplement of fruit was given to a group of 30 individuals, for the purpose of increasing the bulk in the diet. This addition to the usual diet consisted of 12 prunes, 2 apples and 2 large size bananas daily, for 3 days. During the pre-experimental period, 19.3% of these subjects had excessive mucus, 25% had mucous strings, and none had protein. During the period of

high fruit intake, mucus in excess of 0.1 cc./Gm. of stool was found in 12.9%, strings in 29%, and protein in none. During the after-period, mucus above 0.1 cc./Gm. was found in 9.8%, strings in 25.8%, and protein in none (Table IX).

VIII Test with Prostigmin Bromide

Thirty individuals were given 15 mg. of prostigmin bromide, t.i.d., for 2 days. Of these 30 normal subjects, 17% had mucus in excess of 0.1 cc./Gm., 40% had mucous strings, and none had protein during the preliminary period. During the period of drug ingestion, excessive mucus was found in 23%, strings in 27%, and protein in 3.3%. Excessive mucus was present during the post-medication period in 3.3%, strings in 10%, and protein in none (Table X).

DISCUSSION

The results revealed in Table I confirm our previous observations that, at times, normal individuals, free

TABLE VI
Karaya gum period (30 cases)

Periods	No. Days of Observation	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms.	No. of Stools	Percentage of Moisture	Chemical Mucus in cc. Per Gm. of Stool	Chemical Mucus More Than 0.1 cc.	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary	3	92	06	74.4	0.055	16.66	30	0			
Karaya Gum	2	144	118	78.4	0.045	13.33	60	0	36.66	50	50
Post	2	125	110	74.7	0.049	10.0	30	0			

TABLE VII
Magnesium sulfate period (31 cases)

Periods	No. Days of Observation	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms.	No. of Stools	Percentage of Moisture	Chemical Mucus in cc. Per Gm. of Stool	Chemical Mucus More Than 0.1 cc.	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary	3	92	05	74.3	0.057	19.4	29.0	0			
Magnesium Sulfate	2	203	143	83.5	0.051	12.9	22.6	0	55	55	93.5
Post	2	01	103	76.0	0.061	16.1	22.6	3.2			

TABLE VIII
Aromatic fluidextract of Cascara Sagrada period (31 cases)

Periods	No. Days of Observation	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms.	No. of Stools	Percentage of Moisture	Chemical Mucus in cc. Per Gm. of Stool	Chemical Mucus More Than 0.1 cc.	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary	3	92	05	74.3	0.057	19.35	25.8	0			
Cascara Sagrada	2	138	118	76.7	0.066	22.58	32.26	3.23	12.0	35.45	69.29
Post	2	09	05	73.0	0.063	12.9	25.8	0			

from gastro-intestinal symptoms, may show abnormal stool constituents. In other words, a percentage of apparently normal subjects show variations in the pathologic limits of stool constituents. We note, for instance, that of 172 symptomless individuals, mucus in excess of 0.1 cc/Gm was present in 21% mucous strings in 22%, and protein in 4%.

This observation establishes it as a fact that the

occasional presence of "abnormal" constituents in the stool of normal individuals is not necessarily of pathognomonic significance and is not invariably a sign of colon irritation, or the result of the ingestion of a drug at the time the examinations are made. It also emphasizes the possibility of error that may occur in the diagnosis of colitis on laboratory findings, since even the presence of constituents considered abnormal

TABLE IX
High fruit period (31 cases)

Periods	No Days of Observation	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms	No of Stools	Percentage of Moisture	Chemie Mucus in cc Per Gm of Stool	Chemie Mucus More Than 0.1 cc	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary	3	02	05	74.3	0.057	10.35	25.8	0			
High Fruit	2	125	1.18	75.9	0.060	12.00	20.0	0	6.45	32.26	48.4
Post	2	07	00	74.7	0.059	9.68	25.8	0			

TABLE X
Prostigmin bromide period (30 cases)

Periods	No Days of Observation	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms	No of Stools	Percentage of Moisture	Chemie Mucus in cc Per Gm of Stool	Chemie Mucus More Than 0.1 cc	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary	4	95	0.99	73.9	0.055	16.7	40	0			
Prostigmin Bromide	3	118	1.20	76.4	0.059	23.3	26.7	3.3	20	43.3	43.3
Post	1	91	1.14	71.5	0.058	3.3	10	0			

TABLE XI
Summary of medication periods

Periods	No of Cases Studied	Daily Average of				Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms	No of Stools	Percentage of Moisture	Chemie Mucus in cc Per Gm of Stool	Chemie Mucus More Than 0.1 cc	Strings	Protein	Cramps	Flatulence	Laxative Effect
Preliminary (1)	172	09	1.04	73.9	0.055	21.37	22.14	4.1			
Phenolphthalein 0.05 Gm White (2)	122	132	1.20	77.1	0.065	20.47	18.8	4.95	19.53	32.7	44.0
Phenolphthalein 0.12 Gm White	115	161	1.28	70.3	0.061	12.67	15.83	0.83	30.56	38.0	69.5
Phenolphthalein 0.06 Gm Yellow	114	150	1.30	79.2	0.063	17.50	13.95	2.02	37.70	42.5	73.12
Bran 1 oz. (3)	50	121	1.13	75.5	0.058	20.0	24.0	10.0	8.0	12.0	44.0
Maclin K 20 Gm (4)	30	144	1.18	78.4	0.046	13.33	60.0	0	36.66	50.0	60.0
Magnesium Sulfate 15 Gm (5)	31	203	1.49	83.5	0.051	12.9	22.5	0	55.0	55.0	63.5
Cascara Sagrada 4 cc. (6)	31	138	1.18	76.7	0.056	22.58	32.26	3.23	12.9	35.48	61.29
Prostigmin Bromide (7) 0.015 Gm per tablet (6 tablets)	30	118	1.20	76.4	0.059	23.3	26.7	3.3	20.0	43.3	43.3
High Fruit Diet (8) 12 prunes 2 apples 2 bananas	31	125	1.18	75.9	0.060	12.9	20.0	0	6.45	32.26	48.4

- (1) Preliminary period when no medication was given.
- (2) Medication taken in evening. Stool collection started soon after dose.
- (3) Bran ingested daily for 3 days.
- (4) Maclin K (20 Gm) given daily for 3 days. Stool collection started 24 hours after first dose.
- (5) Magnesium Sulfate (15 Gm) given in A.M. Stool collection started immediately after dose.
- (6) Aromatic fluidextract of Cascara Sagrada (4 cc) given in evening. Stool collection started after dose.
- (7) Prostigmin Bromide (15 mg Lid) for 2 days. Stool collection started after dose.
- (8) High fruit diet taken daily for 3 days. Stool collection started 48 hours after first fruit meal.

does not establish with absolute accuracy the existence of colon irritation or colitis

Comparing the stool constituents of our test subjects during the preliminary period with those found during the test periods, when medication or fruit was taken, there certainly does not appear a wide discrepancy in the figures obtained (Table XI). As results of daily stool examinations, before and during the ingestion of various laxative medications, the above figures certainly do not reveal impressive variations in the composition of the stools, at least, not with sufficient constancy to consider these medicinal substances inimical to the colon. Moreover, when we

compare the results with phenolphthalein to those with other substances, we again fail to discover marked differences in the results (Table XII).

In Table XIII are shown the results revealed by examination of the stools obtained from the 31 individuals who received all the test substances. During the first preliminary period, increased chemic mucus in excess of 0.1 cc/Gm was found in 32% of the specimens of stool examined, during the three test periods with phenolphthalein, excess mucus was present in only 29%, 9.7%, and 22.6%, respectively. Mucus strings were found in 25.8% during the preliminary period, but during the three test periods it

TABLE XII

*Summary of post-medication periods —
Comparing the preliminary findings (numerator) with those of post-period (denominator)*

Periods	No Cases Studied	Daily Average of			Chemic Mucus 1h cc. Per Gm. of Stool	Percentage of Cases Having		
		Stool Wt. in Gms	No of Stools	Per Cent of Moisture		Chemic Mucus More Than 0.1 cc	Strings	Protein
Phenolphthalein 0.06 Gm white	122	90	1.08	73.7	0.054	21.94	23.02	2.50
		104	0.02	75.0	0.062	15.7	18.86	4.17
Phenolphthalein 0.12 Gm white	115	07	1.01	73.3	0.062	21.33	16.67	1.67
		07	1.01	75.0	0.06	15.5	17.5	1.67
Phenolphthalein 0.06 Gm yellow	114	07	1.05	73.6	0.062	16.25	10.37	2.50
		02	1.03	74.2	0.066	17.20	14.58	2.50
Dran	50	100	1.08	74.3	0.067	20.0	20.0	8.0
		82	0.02	73.5	0.056	24.0	18.0	8.0
Karaya Gum Period	80	02	0.06	74.4	0.058	16.66	30.0	0
		125	1.10	74.7	0.049	10.0	30.0	0
Magnesium Sulfate	31	02	0.05	74.3	0.057	10.4	29.0	0
		01	1.03	76.0	0.061	16.1	22.6	8.2
Cascara Sagrada	31	02	0.05	74.3	0.057	10.35	25.8	0
		00	0.05	73.0	0.063	12.0	25.8	0
Prostigmin Bromide	30	95	0.09	73.9	0.055	16.7	40	0
		01	1.14	71.5	0.058	3.3	10.0	0
High Fruit Diet	31	02	0.05	74.3	0.057	10.35	25.8	0
		07	0.00	74.7	0.060	0.58	25.8	0

Preliminary Period—Time before any test substance was taken

TABLE XIII

Comparison of stool findings after various medications in the same individuals

Periods	No Days of Observation	Daily Average of			Chemic Mucus In cc Per Gm of Stool	Percentage of Cases Having			Subjective Symptoms		
		Stool Wt. in Gms	No of Stools	Percentage of Moisture		Chemic Mucus More Than 0.1 cc.	Strings	Protein	Cramps	Flatu- lence	Laxative Effect
Preliminary	3	112	1.15	74.0	0.054	32.3	25.8	3.2			
0.06 Gm white Phenolphthalein	2	135	1.17	77.4	0.065	20.0	16.1	3.2	12.0	35.5	33.7
Post	2	09	1.03	75.0	0.050	16.1	10.4	3.2			
0.12 Gm white Phenolphthalein	2	165	1.27	78.5	0.060	9.7	15.1	3.2	35.5	38.7	74.2
Post	2	101	1.04	75.7	0.059	22.6	19.4	0			
0.06 Gm yellow Phenolphthalein	2	151	1.36	79.5	0.067	22.6	12.0	0	35.5	41.0	83.9
Post	2	83	1.07	73.1	0.058	25.8	25.8	3.2			
Preliminary	3	92	0.6	74.4	0.058	16.66	30	0			
Karaya Gum	2	144	1.18	78.4	0.046	13.33	50	0	36.66	50	60
Post	2	125	1.10	74.7	0.049	10.0	30	0			
Magnesium Sulfate	2	203	1.48	83.5	0.051	12.9	22.6	0	55	55	93.5
Post	2	91	1.03	76.0	0.051	16.1	22.6	3.2			
Cascara Sagrada	2	138	1.18	76.7	0.056	22.58	32.26	3.23	12.9	35.48	69.29
Post	2	99	0.6	73.0	0.053	12.0	25.8	0			
High Fruit	2	125	1.18	75.9	0.060	12.90	20.0	0	5.45	32.26	48.4
Post	2	07	0.90	74.7	0.050	9.68	0				
Prostigmin Bromide	2	118	1.20	76.4	0.050	23.3	26.7	3.3	20	43.2	43.3
Post	1	91	1.14	71.5	0.058	3.3	10	0			

was present only in 16%, and 13% respectively. Before the tests, protein was found in the stools of 32% of these subjects, while the test periods yielded 33% in the first 33% in the second, and none in the third test period.

Following an interval of rest for several weeks, the subjects had another stool examination, during which mucus above the postulated normal was found in 16.6% of the specimens, mucous strings in 30%, and protein in none. During the test periods that followed, mucus above 0.1 cc/Gm of stool appeared in 13 to 23%, strings in 23 to 60%, and protein in 0 to 33%. It is noteworthy that protein was found only after prostigmin and after cascara—in the second half of the experiments. As a result of these examinations, again a comparatively small difference was evident between the stool constituents during the preliminary and test periods.

We also had an opportunity to study the constituents of the stools obtained from 119 patients hospitalized for various ailments. For the purpose of this test, they were given 0.1 Gm (about 1½ grains) of USP phenolphthalein in a 33% alcoholic elixir. In this group, increase in mucus in the stools was found in 41%, mucous strings in 22.7%, and protein in 11.8%. In comparison, 322 patients serving as controls who had not received phenolphthalein, exhibited excessive mucus in 6.2%, strings in 15.2%, and protein in 11.5%.

Table XIV is a tabulation of results of periodic examinations of stool specimens obtained from patients who were accustomed to taking 0.3 Gm (5 grains) of USP phenolphthalein almost daily for weeks or months, in comparison with another group of patients who took a variety of other laxatives. No considerable variation is evident between the two groups, nor is there apparent a marked variation between the stool constituents of the patients who were taking phenolphthalein more or less continuously as compared to those who have taken 1 to 3 doses for the purpose of these observations. Our findings in this respect are

at variance with the reports published by others (3). Venturing a reason for this, we are of the opinion that our more extensive stool examinations have eliminated from consideration those cases which, as a result of less exacting stool examinations, may have been classified as suffering from colitis. When it is kept in mind that 20% of normal individuals (medical students), hardly in the age group where colitis is most frequently encountered, had mucus in excess in the stools, that 20% of them had mucous strings, and that 8% had protein, it is obviously unjustified, to apply the diagnosis of colitis to any individual who presents at times pathologic constituents in the stools. Even though the presence of excessive mucus, strings and protein in these normal subjects gave no rise to symptoms, it is questionable if the diagnosis of colitis would have been sufficiently supported, the findings in the stools notwithstanding, even had they been conscious of some vague abdominal symptoms. The symptom complex of colitis manifests itself with greater definiteness on the general health and well-being of the patient.

Proctosigmoidoscopic examination was not made in any of the normal individuals. This procedure was, however, carried out on some of the patients who took phenolphthalein regularly over a prolonged period. These patients included cases of chronic peptic ulcer, and gall bladder disease who had constipation of many years duration and who, therefore, resorted to various laxatives. Contrary to expectation, proctosigmoidoscopy in these cases revealed a pale, atrophic-appearing mucosa, and not a red and congested membrane that would have indicated a condition of irritation. In some instances, there was a resemblance to the atrophic gastric mucosa seen by gastroscopy. In our series of patients who were taking phenolphthalein over a long period, neither the proctoscopic findings nor the results of the stool examinations were similar to those described as characteristic of colitis (3).

In the course of previous studies, we have gained

TABLE XIV
Stool findings on patients taking phenolphthalein for a prolonged period

Name	Length of Time Phenolphthalein Was Taken	Total Amount of Phenolphthalein Taken	No. of Stools Examined	Number of Times That Abnormal Stool Constituents Appeared		
				Chemic Mucus More Than 0.1 cc	Strings	Protein
G. G.	0 mos	00 Gm—1350 gr	14	0	0	0
A. J.	7 mos	50 Gm—750 gr	4	0	1	0
J. K.	4 mos	Yellow 16 Gm—240 gr	3	0	0	0
J. M.	12 mos	80 Gm—1200 gr	12	0	3	3*
P. M.	4 mos	40 Gm—600 gr	2	0	0	0
F. McD.	5 mos	40 Gm—600 gr	3	0	0	1
W. R.	8 mos	70 Gm—1050 gr	8	0	0	2
S. T.	6 mos	60 Gm—900 gr	6	0	0	0
W. W.	5 mos	Yellow 20 Gm—300 gr	8	0	0	0
W. W.	8 mos	80 Gm—1200 gr	7	0	1	1

Control cases taking other laxatives

J. J.	9 mos	Mineral Oil Mg O or Cascara	12	0	2	1
A. L.	0 mos	Same	9	0	2	1
I. M.	6 mos.	Same	4	0	0	0
V. N.	2 mos	Same	1	0	0	0

*Signs of irritation present at various times even before medication

the impression that changes in the bulk and consistency of the stool may be held responsible for certain alterations in its constituents. Since laxatives are taken by people who are constipated, that is, those who, as a rule, have a low bulk residue in the colon, and since laxatives tend to increase bulk, it is possible that increase in the constituents of the stool following the ingestion of a laxative, may be only present in proportion to the extent of changes in the increased bulk and not be due to irritation caused by the laxative taken. In substantiation of this impression, we used no laxative, but a high fruit supplement to the diet alone, in one series of 30 cases, since this may be expected to produce only increased bulk in the colon, and should not produce the irritation often attributed to a drug. Tables XI and XIII show that the changes that have taken place in the stool constituents are not substantially different from those subjected to the influence of other test substances classified as drugs.

It is true, of course, that constipation may occur also in the presence of adequate bulk in the intestine. Indeed, in dyschesia the rectum may actually be so overfilled that the colon is unable to discharge its contents into the rectum. While we have not had an opportunity to examine the stools obtained without the use of a laxative from such cases, there is no reason to believe that the findings would materially differ from those we have examined in the series. It is probable that the abnormal constituents would be present in even greater quantities.

For confirmation of our hypothesis that the appearance of abnormal stool constituents is influenced by changes in bulk rather than by the direct action of the substance introduced into the intestine, we have administered prostigmin bromide, a drug that acts on the nerve endings of the intestine rather than on the mucosa or musculature directly. As shown in Table X, there was an increase in mucus in 23.3%, and protein was present in 3.3% following medication with prostigmin bromide. These findings do not vary greatly from the other results observed.

To obtain a proportionate evaluation of the changes that have occurred following the ingestion of the test substances, we measured the average increase in weight of the stools and their moisture content during the test periods.

We found that under the influence of the varying doses of phenolphthalein, the average weight of the stools increased by 33.3, 64.9 and 63.9%, respectively, during the three tests made with phenolphthalein. The average moisture content increased from 73% originally to 79%, during the test period, an increase that tends to change quite considerably the physical characteristics of the stool. During the bran period, the weight of the stools increased 21%, while the moisture changed from 74.3% in the preliminary period to 75.5% during the test period. Following the administration of karaya gum (mucin-K), the weight increased 56%, while the moisture of 74.4% rose to 78.4%. Magnesium sulfate caused a weight increase of 54.7%, and increase in the moisture from 74.3% to

83.5%. The administration of cascara sagrada was responsible for a weight increase of 50%, and a rise in the moisture content from 74.3% to an average of 76.7% before, to 76.4% during medication. The high fruit supplement to the diet brought a 36% increase in the weight of the stools, and a rise of moisture content from 74.3% originally to 75.9% during the test period.

No direct relationship became evident between the increase in weight or rise in moisture content in the stools, and the appearance of abnormal constituents as a result of this relationship. That is, increase in weight was not necessarily attended by a corresponding increase in moisture content. Similarly, the quantity of solid or liquid constituents was apparently not a determining factor in the proportionate quantities of abnormal constituents present, a smaller or larger percentage could be present, irrespective of changes in bulk or moisture. In the majority of instances, however, the abnormal constituents appeared in a higher percentage of cases following the ingestion of those test substances which produced the least rise in the weight or moisture content of the stools. This would tend to the confirmation of our previous findings reported elsewhere (4), that low bulk in the colon may give rise to signs of irritation.

In the course of this investigation, we also studied the subjective symptoms and the intensity of laxative effect resulting from the administration of each test substance, in order to determine whether a correlation exists between subjective symptoms, laxative effect, and the appearance of abnormal constituents in the stool. The subjective symptoms were reported by each individual participating in the test on a "questionnaire sheet" provided for the purpose. Cramps and flatulence were the two most frequent symptoms reported. The term "cramps" was used to designate abdominal discomfort produced by a rhythmic griping, but not severe pains. Flatulence denoted mainly a fullness in the abdominal region, associated with moderate, general, indefinite discomfort. From Table XIII it is evident that cramps occurred more frequently following the ingestion of substances resulting in a high percentage of laxative effect, while flatulence was, as a rule, not associated with such an effect. No correlation was found between the presence of excessive mucus, or mucous strings, or protein, and the appearance or absence of cramps or flatulence. The laxative effect was also unrelated in any discernible way to the findings of abnormal stool constituents.

As previously mentioned, preliminary stool examinations in 322 patients with various diseases showed increase in mucus in 62%, mucous strings in 15.2%, and protein in 11.5%. In contrast to these findings, the preliminary tests of stool specimens of 58 patients, who complained of constipation, showed excessive mucus in 21%, strings in 21%, but no protein. In the latter group, if we separate those patients who had stools of very low bulk, we find that excessive mucus was present in 43%, and strings in 22%. Similarly, it

was found that normal individuals with stools of low bulk, have mucus in excess of the normal, and strings are found more often than in those whose stools approximate the average normal. In this study, based on previous observations, the normal bulk, by weight, was considered to be between 75 and 120 Gms a day.

The rather high incidence of abnormal stool constituents at various times in apparently normal individuals and in patients not presenting obvious gastro-intestinal pathological conditions, makes it difficult to evaluate accurately the importance of those constituents. It certainly cautions against the ready application of "colitis" to a case that presents abnormal constituents in an occasional stool specimen, or even on repeated examination. Too many factors, some known (changes in bulk, for instance) and others yet undetermined, influence the composition of the stool, so that no clear-cut diagnostic evaluation is possible from the physical and clinical characteristics of the stool alone. Similarly, the influence of drugs acting on the intestines, such as laxatives, should be evaluated with more than ordinary care, so as not to attribute certain independently occurring changes to the effect of the drug. The occasional appearance of abnormal stool constituents in the feces does not warrant the diagnosis of colitis or even colon irritation, only the persistent presence of abnormal constituents in the stools (mucous strings and protein) may be justifiably considered indicative of a pathologic condition of the intestinal mucosa. However, even in such instances, the possible influence of other factors, such as fissures, hemorrhoids, must be ruled out.

The possibility of abnormal constituents appearing in the stool following the intake of a laxative, should not be a deterrent from administering a laxative whenever the need for it exists. A large number of factors may lead to a temporary constipation. This temporary derangement of the bowel habit can usually be readily controlled by the ingestion of a suitable laxative during the period when measures are instituted for the removal of the causative factor. To assert that the use of a laxative is fraught with danger, is obviously as erroneous a therapeutic conception as to keep on giving laxatives to people with constipation, without endeavoring to discover the cause of the derangement, and removing it. Laxatives are useful drugs, indicated as a therapeutic measure in certain conditions (5) and at certain times. Variation in their effect in different individuals and at different times, has resulted in the production of a number of such substances, each of which acts supposedly in a different, more optimal way. The occasional use of a laxative should not be unnecessarily discouraged, rather the

public needs to be enlightened about the "when and how" of their rational use.

SUMMARY

From the results obtained from numerous examinations of stool specimens from normal individuals and patients, with and without evident gastro-intestinal involvement, and before as well as after the ingestion of various test substances, the following conclusions appear justified at the present time.

1 Abnormal stool constituents (excessive mucus, mucous strings, and protein) appear, at one time or another, in a fair percentage of patients, regardless of whether gastro-intestinal symptoms are or are not present. (Cases definitely diagnosed as "colitis" are not included in this series.)

2 Changes in the bulk of the stool and the type of diet seem to influence the occurrence of abnormal stool constituents. Stools of hard, low bulk more often contain abnormal stool constituents.

3 Following the ingestion of various drugs and of bulk producing substances employed as laxatives, no appreciable changes appeared in the constituents of the stools examined, in a few instances where the observation was extended over a more prolonged period, the changes were no less unimpressive.

4 No correlation was found between the degree of laxative effect, presence or absence of subjective symptoms (cramps and flatulence) and the finding of abnormal constituents in the stools.

5 The occasional finding of abnormal constituents in the stool of an individual does not justify the diagnosis of "colitis," nor does it warrant attributing the findings to any medication previously ingested.

6 Since there is no evidence that the occasional use of laxatives produces colitis, their use should not be summarily prohibited, but the public should be enlightened as to when and how to use them.

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The Tired, Weak, Exhausted, Depressed Patient

By

JOHN A. TURNBULL, M.D.
BOSTON, MASSACHUSETTS

THE tired, weak, exhausted, toxic, depressed patient who drifts from one physician to another, meanwhile growing progressively worse, is often induced to secure operative relief. The syndrome is unmistakable but some infection or other is supposed to be at the seat of the trouble. Gall bladder, appendix, tonsils, teeth, and female pelvic organs are frequently removed, especially the gall bladder, as this seems to be considered a menace. Faith is put in such operations to effect a complete restoration of health, but disappointment follows and as the result of the added strain of the surgical procedure the patient finds himself weaker, more tired, exhausted, toxic, and with the system even more depressed. Tonsils and teeth are in many cases hopelessly sacrificed, without definite evidence of the source of trouble. Such needless operative work has the effect of lowering the patient's power of resistance and bringing about an increased depression.

Failing to improve under the physician's treatment, the patient is then invariably told that his symptoms are all mental, imaginary, neurasthenic, or hypochondriac. Such a diagnosis is often conveyed to the relatives who believe this to be the case, especially as the patient has consulted numerous excellent medical men, and the surgical work was done by men of highest reputation. After the diagnosis, the physicians, relatives and friends tell the patient to snap out of it, to help himself, to get out among people, to attend social affairs, to become interested in their business. But this means additional strain and effort, the patient becomes more tired and weak, and there is markedly increased toxicity. The depression has now reached the stage of suspected insanity and despair of regaining health.

The patient may be a mother who had reached such a condition that she neglects her household duties, her husband and children sadly, spends her time in bed much of the time with tears trickling down her cheeks, realizing that she is not the companion for her husband as formerly, and that she cannot care for her children and give them proper love and attention. In the case of the man who has lost his grip on business, who is unable to concentrate or work as before, who cannot do things formerly easy for him, unable to overcome obstacles once simple and a pleasure for him to overcome, it causes him to realize his plight. With the strain of business under the economic conditions

of the past five years, it is no wonder that many men and women afflicted with toxic allergy, but ignorant of the simple means of cure, have committed suicide.

Theirs are not imaginary symptoms, they are not just neurasthenic, hypochondriac or neurotic cases for the physician to pass over with little attention. They are ill of a definite clinical entity, and they are very sick, though many of their symptoms bear a similarity to those described under neurasthenia and hypochondria in our great medical text books.

However neurasthenia is a term having a rather indefinite meaning. It designates very unlike conditions and is frequently used by the physician when unable to trace the etiological factor. Burr defines neurasthenia as

1 Only a condition of pathological weakness, without discoverable lesions, showing itself by too rapid and too great fatigue, physical, mental, or both, and emotional unbalance and undue irritability, and too great response to stimuli of the nervous system.

2 Inability or disability more than perversion of function.

The author classifies these toxic cases under

(a) inability

(b) disability and

(c) perversion of function, due to hypersensitivity to certain foods.

These people suffer and need care and treatment to correct the underlying cause or causes of their troubles. Just as much attention should be paid to their symptoms as if they were victims of pneumonia, appendicitis, or any other disease entity. Having the opportunity to treat many of these patients, with excellent results, the author designates the syndrome of the tired, weak, exhausted, depressed, toxic patient as toxic allergy.

The symptoms of these patients are many, and may be manifest in all parts of the body, literally from the hair of the head to the toes. For example, the hair may be dry, brittle, coarse and unmanageable, causing the patient to be unable to keep the hair dressed properly, or occasionally there may be extremely oily hair. The symptoms may extend to the toes and many complain of pains and aches in the feet and toes (1).

Headache is a common complaint, the condition being described as "a confused head," a miserable feeling in my head," "with dull pressure," a "tightness," a "feeling as though my head would burst," and these patients are unable to concentrate on business, writing, or anything that they may undertake. They are disturbed by people, by crowds, and are unable to

Editor's Note While food allergy cannot be regarded as the sole cause of disease, Dr. Turnbull proves his contentions by case reference. All can agree with him that the full importance of food allergy has not as yet been realized.

maintain conversation or understand what people say

A confusion of ideas and a confused mind, is followed by a consciousness of greater weakness and depression. Many of these patients formerly with wonderful dispositions, calm, happy, cheerful, and thoughtful of others, and now in this cloudy, blank, confused condition, become very irritable and misunderstand the good intentions and acts of their family and friends.

All such patients say that their eyes have a heavy feeling, with pressure at the back of the eyes, as though they were being pushed out. They do not want to read, write, or do anything that strains the eyes, for fear of visual disturbance, and thus mental confusion.

The taste is affected and is described by the patient as "a brown taste," or "as a horrible taste like sewerage." Many have a collection in the mouth of white, sticky, cotton-like mucus, which sometimes difficult to clear out. Some describe the tongue as big, or as too large for the mouth. The tongue usually had a thick coating, varying in color from yellow to dark brown. Many complain of a dry and sore throat, with a dry hacking cough, frequently raising a thick sticky mucus or a gelatinous mucus on rising in the morning and occasionally a thick sticky mucus during the day.

Digestive complaints are common to these patients (2). Distress may be felt over the whole abdomen (3), especially marked in the epigastrium. They have an all-gone feeling, and an aching, with a fullness and distention, quite marked in the upper half of the abdomen, and greatest in the right hypochondrium. Patients who have had a cholecystectomy state that they expected to be free from all symptoms following the operation, but that the symptoms of weakness, the tired condition, exhaustion, depression and abdominal symptoms became worse immediately thereafter.

Although these patients spend much time in bed, they sleep poorly, disturbed by dreams, confused ideas, and in the morning feel "all in," completely exhausted, indeed hardly able to move. They do not seem to get enough sleep and rest.

Many declare that their bowels are constipated, others that although the bowels move daily the movement is insufficient for comfort.

Occasionally some of these weak, tired, toxic, depressed patients are still working or attempting to work, accomplishing little, yet not quite compelled to give up their labors. If they continue under the usual regimen, the time will soon come when they will be forced to stop working, and this fear is constantly before them. It is these border-line break-down cases, who are advised to take a vacation or adopt a change of work in the hope that new environment and contacts will remedy the condition. Some may return slightly better, but in a short time retrograde. Others come back with all symptoms increased because of the effort made to change routine ways of working, or from the fatigue of traveling and meeting strange people, and also because they miss the comforts of home. Others of these patients have not worked for

years, being unable to carry on, spending much time in bed from extreme exhaustion and miserable feeling, described as of not only the head but all over the body.

These people have undergone great changes in disposition. In some, these changes have developed so gradually that relatives and friends have failed to notice their inability to carry on their duties until the break-down point has arrived.

On close questioning of these patients, one finds that the onset of the trouble took place some time before realization of the symptoms, and thus the patient's illnesses are not of a few weeks', but of months' or possibly years' duration.

With the symptoms as stated, one can frequently trace hereditary influences, which may manifest themselves in the same form or in others closely related. Specific antibodies can be demonstrated in the blood of individuals inheriting such allergic peculiarities and in them the skin demonstrates quite a constant reaction to food excitants through abrasion of the skin (4). Hereditary influences are those carried by the germ and sperm cells from generation to generation, but other influences may arise and act after the fusion of these cells, such as an infectious condition following conception. These influences may manifest themselves at an early age or be delayed until later in life. We come into the world with unequal powers of resistance to intellectual, emotional, physical or chemical stress. Stress is the sum of all forces which act on the individual organism and its constituent cells. This includes diseases, the wear and tear of life, everything affecting the emotions, mechanical work, and intellectual effort. While the majority of people are able to resist ordinary stresses and strains, many succumb. The chief cause seems to be an hereditary tendency to a disease. Fortunately, these types are susceptible to only a limited class of irritants (5). No remedy has been discovered to neutralize or counteract the specific response to the recognized specifically toxic allergens, but omission of the excitant factor is equivalent to a cure.

CASE HISTORIES

Case 1. Male, aged 40, a bookkeeper in a banking and brokerage business. As a child was not strong, had digestive troubles, upset stomach at intervals, easily tired, poor appetite, enlarged cervical glands, posterior to the sterno-cleido-mastoid muscle, many of which formed abscesses and at present show scars. At fourteen years of age was free from all the above symptoms and was able to play and do things with other boys of good health. Patient continued in good health until the age of 38. During the war the patient worked in the banking business, and as this concern was short of help and handled government Bonds, many of their employees were forced to work sometimes all night and holidays. Many of the employees of this firm gave out completely.

This patient on consultation was tired, exhausted, depressed, and had a "mean" feeling all over, a miserable feeling in the head hard to describe, and could not think, to move was an exertion, in getting out of

Case 3 The author was consulted by patient on September 12, 1927, for a weak, tired, exhausted condition, which started the previous June. These symptoms increased to such an extent that by August she was completely exhausted and wanted to stay in bed. The slightest exertion required great effort and caused an intensification of her symptoms.

Patient had a cough, foul odor to the breath.

Laboratory findings Hemoglobin, 85%, white blood count, 6,700, red blood count, 4,320,000, polymorphonuclears, 53, lymphocytes, 31, transitionals, 3, mononuclears, 7, eosinophiles, 8, mast, 1, red blood cells normal size, color and shape, platelets, normal, fasting blood sugar, 78 mg per 100 cc of blood, tolerance blood sugar 84 mg per 100 cc of blood (1½ hours after 100 grams dextrose), blood calcium, 11.3 mg per 100 cc of blood; Wassermann doubtful, another Wassermann on Oct. 1, 1927, negative, fasting urinalysis, clear, pale, acid, 1010, albumin, none, sugar, none. Sediment a few squamous cells, an occasional round cell and a rare leucocyte, tolerance urinalysis same as fasting urine (1½ hours after 100 grams dextrose) basal metabolic rate, minus 8, blood pressure, systolic, 112, diastolic, 70.

The doubtful Wassermann reaction on September 12th was probably due to the allergy disturbance in the system, as the Wassermann on October 1st was negative after eliminating the effects of the allergy disturbance.

This patient was put on diet and at the next visit, September 29, 1927, she showed decided improvement from the tired, weak, exhausted, and depressed symptoms. By October 10, 1927, the patient was free from all symptoms, had much energy and felt like doing things. There was no odor to the breath, and the tongue had a normal appearance. Systolic blood pressure was 120, and diastolic 75.

Case 4 Female, mother of case 3, aged 52, reported January 4, 1926, feeling tired, weak, exhausted, depressed, with headaches since ten years of age, which have steadily increased. Had asthma from two years of age until the age of thirty-one. Uremia at eighteen years of age, and arthritis at forty-six. Headaches are continuous and so severe as to confine the patient to bed three or four days out of every week, and they are accompanied with violent epigastric pain which requires morphine hypodermically. The patient is all used up for three or four days following these severe attacks. Does not feel well more than three days out of every month. As an illustration of the patient's forgetfulness and confused mental condition owing to generally miserable feeling, she would go to the railway ticket office and walk away without the ticket or change. This confused state of mind had rapidly increased in the last six months. Blood pressure Systolic 130, diastolic 80.

Patient was put on a diet arranged by the cutaneous tests and she was relieved of all symptoms. She had tried many other forms of treatment but this is the only one that had given relief.

Case 5 Age 61. In August, 1933, this patient, while driving home from his work with his son, was suddenly seized with severe pain in the chest, gasped for breath, and fell unconscious to the floor of the car. This was diagnosed as a coronary occlusion. He was seriously ill and was attended by cardiologists. The patient recovered after a long illness. In May, 1934, his

daughter said that he was about the house and would go out in the yard but wanted to sit around all the time, was very cross, irritable and cranky, and difficult to live with. On June 16, 1934, his wife telephoned that she did not know what to do with her husband, that he was cross, irritable, depressed, and did not want to do anything. She said that he had originally been a very peaceful man, easy to get along with, and never complained of anything.

On June 19, 1934, the man consulted this office. A complete change had taken place in one year in his general appearance and actions. The statements of both his wife and daughter were in confirmation.

Laboratory findings Hemoglobin, 95%, white blood count, 8,200, red blood count, 5,110,000, polymorphonuclears, 59, lymphocytes, 33, eosinophiles, 8, fasting blood sugar, 90 mg per 100 cc of blood, tolerance blood sugar, 123 mg per 100 cc of blood (1½ hours after 100 grams dextrose), blood uric acid, 4.7 mg per 100 cc of blood, fasting urinalysis, pale, cloudy, acid, 1016, albumin, slightest possible trace of sugar, partial reduction. Sediment many pus cells, basal metabolic rate, minus 7, blood pressure, systolic, 120, diastolic, 75.

This patient was put on diet and in one week he felt, acted and looked entirely different. The irritability, crankiness, crossness and depression were decidedly less, so much so that all his friends remarked the transformation. In two weeks he was the bright and cheerful man he had formerly been.

In October, 1934, a letter was received from this man stating that he was well and that he was working every day, and that the cardiogram taken one week before showed a distinct improvement over that of six months previous.

Case 6 Female, age 43. The author consulted December 13, 1922. Her symptoms at this time described her as weak, tired, depressed, mentally confused with a feeling of abdominal distention, noises in the ears as roaring, sizzling, steam letting off, and pains all over the body, from head to toes. On account of the abdominal distention and distress she was advised by physicians to have her gall bladder and appendix removed, which operations were performed in March, 1920. After these operations the patient's condition grew rapidly worse, with increasing weakness, exhaustion, depression and confusion. Talking with people caused her mental confusion and the patient was unable to answer questions intelligently. Since January 19, 1922, has had a tendency to fall either to the right or to the left, this condition came on suddenly, and on standing with the feet together, eyes closed, the patient would sway in a wide angle and it was necessary for someone to be by the patient to keep her from falling. Vertigo would start on her getting out of bed, rising from a sitting position. In August and September, 1922, was nauseated for seven weeks, vomiting mucus and bile every morning. On August 19 patient had eaten oysters and this was followed in eight hours by marked swelling of the face, eyelids, and an aching all over the body. Patient then avoided the foods to which she was sensitive and in ten days the abdominal symptoms were relieved and with it the train of symptoms, such as of weakness, tired feeling, depression, and mental confusion. If this patient were to eat any of the foods to which she is

sensitive, the symptoms would return. The patient returned to her work as a nurse and now, thirteen years after, is well and continuing her work.

Case 7 Male, aged 29, single, consulted this office May 14, 1928. Always sick as a child and has been in poor health all his life, had never been strong. Lost twenty-six pounds in weight in six months, always weak, tires easily, mentally confused and depressed. For one year had suicidal and homicidal tendencies, trying at times to take his own life and that of his attendant, trying himself to jump out of windows, and threatening his attendant with andirons while the latter was taking a bath. This mental clouding became worse after the sale of his home fifteen months, previously, the home having been sold in order that he might be near the city and his relatives. Some dizziness at intervals for one year, a feeling of falling forward when walking, with a swaying to either right or left. Feels so tired and exhausted that he is not inclined to get up in the morning. After being up a little while, feels a little better, after one o'clock, is completely tired and exhausted and has to lie down, after eight p. m., completely exhausted.

The author had previously heard about this patient from the patient's aunt, who was being treated at the time for arthritis and hypertension. She said that she was worried because they had been obliged to place him in an insane institution for treatment. While in this institution, the patient made an attack on a male nurse, and in order to protect himself the nurse was obliged to knock the patient out. On account of this attack, the patient was removed from the institution and was placed in a suite in a hotel under guard of his attendant.

Laboratory findings: Hemoglobin, 85%, white blood count, 6,000, red blood count, 5,320,000, polymorphonuclears, 65, lymphocytes, 23, mononuclears, 2, transitionals, 5, eosinophiles, 1, basophiles, 4, red blood cells show slight variation in size, fasting blood sugar, 94 mg per 100 cc of blood, tolerance blood sugar ($1\frac{1}{2}$ hours after 100 grams of dextrose), Wassermann, negative, fasting urinalysis, normal, clear, acid, 1,014, albumin, none, sugar, none, sediment one finely granular cast, a rare leucocyte, round and squamous cell and a little mucus, tolerance urinalysis, pale, clear, acid, 1,004, albumin, none, sugar, slightest possible trace. Sediment on occasional red blood cells, a rare leucocyte, round and squamous cell, basal metabolic rate, minus 25, blood pressure, systolic, 160, diastolic, 70.

Cutaneous tests were made to find the foods contraindicated for this patient. On June 12, 1928, after following the diet, patient was feeling better, sleeping better, not tired, less mental confusion, no suicidal or homicidal acts during the last ten days, and continued to improve so that by July 1, 1928, the patient said "I am in the best condition physically and mentally that I have ever experienced," a statement which was corroborated by his attendant.

The patient's financial affairs were managed for years by a trustee, who was a lawyer and an uncle of the patient. The author received a communication from this trustee asking his advice regarding the ability of this man to manage his own affairs, and asking him if possible to write a letter endorsing his capability, in order that the trustee might go before

a judge and ask for a transfer of management. The transfer was accepted by the court, and the patient on taking charge of his financial affairs and other business, felt delighted at the change of his condition.

This patient started life with much illness as a child and with an allergic history of urticaria at intervals all his life, and again for fifteen years, which was another form of allergy. He was always weak, tired, exhausted, depressed, and had mental confusion since fifteen years of age, and later on this apparent neurosis was intensified, as shown by his suicidal and homicidal acts.

Case 8 Female, of 67, a widow, consulted the author June 11, 1935. She had a sense of weakness, fatigue, exhaustion and general depression which began in 1931 and continued ever since, being much worse in the morning and up until noon. At the present time of consultation she was never free from these symptoms. The depression came in waves and the bad spells developed suddenly with a sleepy stupor, a confused mind, and as the patient expressed it, "might be losing my mind completely."

Laboratory findings: Hemoglobin, 90%, white blood count, 8,700, red blood count, 4,100,000, polymorphonuclears, 60, lymphocytes, 22, mononuclears, 7, transitionals, 2, eosinophiles, 6, basophiles, 3, fasting blood sugar, 160 mg per 100 cc of blood, blood uric acid, 7.2 mg per 100 cc of blood, non-protein nitrogen, 36.8 mg per 100 cc. of blood, Wassermann, negative, fasting urinalysis, slightly acid, 1,013, albumin, slight trace, sugar, slight reduction, sediment many pus cells, red blood cells, and squamous epithelium, basal metabolic rate, minus 6, blood pressure, systolic, 178, diastolic, 90.

This patient had a high fasting blood sugar with a trace of sugar showing in the urine, a high blood uric acid, and in the differential count of the mononuclears, eosinophiles and basophiles.

Cutaneous tests were made to isolate the foods to which the patient was sensitive and a diet arranged accordingly. On June 28, 1935, the patient had no bad depression spells and she felt at least fifty per cent improved, more cheerful, no bloated feeling or abdominal distress. On July 9, 1935, the depression was reported gone and also the tired, weak, exhausted feeling. On September 4, 1935, the patient remarked how well she felt. "To think that a diet would cause all this change in my health!" Once the patient ate steamed clams at night and the following morning brought on all the symptoms, along with tickling in the throat, and a cough, with severe pain and swelling in the right big toe. These symptoms all cleared up in forty-eight hours. At the time of the test, clams gave a reaction and the patient was instructed to avoid them, but feeling so well she thought herself immune. The reaction proved to the patient the accuracy of the cutaneous tests. A letter was received from this patient on October 8, 1935, stating that she was bright, cheerful and happy, with no distress or pains, and that she could walk from three to five miles with comfort.

Case 9 Female, aged 39, married, consulted the author on January 14, 1935. Marked weakness, tired, exhausted, fatigued, depressed with indigestion, distress, gas, nausea, dizziness, headache, and a swaying forward and backward, a full feeling in the right ear.

These symptoms started in 1930, and gradually increased, so that the patient had been in bed two years, so exhausted that it was difficult to turn around. In November, 1933, the gall bladder and appendix was excised, this was followed by severe pain in the abdomen, more nausea, gas and distress, with vomiting of dark blood, sometimes bright red. All symptoms increased since removal of the gall bladder and appendix.

The patient felt at the time she would lose her mind completely. Patient was mentally confused, unable frequently to understand what people were talking about, had frequent crying spells, slept poorly, and had bad dreams. Bad taste in the mouth all the time, patient expresses herself "My mouth tastes like sewerage."

Laboratory findings: Hemoglobin, 85%, white blood count, 10,800, red blood count, 4,930,000, polymorphonuclears, 63, lymphocytes, 35, eosinophiles, 2, blood uric acid, 3.2 mg per 100 cc of blood, fasting blood sugar, 90 mg per 100 cc of blood, tolerance blood sugar, 202 mg per 100 cc of blood, Wassermann, negative, fasting urinalysis, small amount, albumin, none, sugar, none. Sediment: an occasional leucocyte, mucus threads and yeast cells, tolerance urinalysis, small amount, cloudy, acid, albumin, none, sugar, complete reduction. Sediment same as before, basal metabolic rate, plus 10, blood pressure, systolic, 100, diastolic, 70.

This patient was tested cutaneously by foods and the proper diet arranged. After some time on the diet, the woman's depression was vastly relieved, she could now smile and laugh and felt like living. After three weeks of this diet, she was relieved of all symptoms of which she had complained. The systolic blood pressure was 120, and the diastolic 70. Here is an increase of 20 mm in the systolic pressure.

In this case there was an increase of lymphocytes, a low sugar tolerance and a complete reduction of the urine in the tolerance test.

This is a case where the patient, though ill previous to cholecystectomy and appendectomy, immediately grew worse following the operations.

Case 10. Female, aged 40, came for consultation November 20, 1928, for weakness, exhaustion, and depression. The weakness, the tired, exhausted and depressed condition, came immediately after an attack of pruritis. All these symptoms were closely linked and all were bad at the same time, with the exception of the exhaustion which was greatest in the morning. On account of her weakness and mental depression, she spent most of the past year in bed. Indeed the patient lost all of her gaiety and her smiling cheerful ways.

Laboratory findings: Hemoglobin, 85%, white blood count, 8,700, red blood count, 4,608,000, polymorphonuclears, 70, lymphocytes, 26, mononuclears, 1, transitionals, 1, eosinophiles, 1, basophiles, 1, fasting blood sugar, 79 mg per 100 cc of blood, tolerance blood sugar, 83 mg per 100 cc of blood, uric acid, 3.83 mg per 100 cc of blood, Wassermann, negative, basal metabolic rate, minus 14, blood pressure, systolic, 87, diastolic, 60, urinalysis fasting, straw, very slightly cloudy acid, 1,008, albumin, none, sugar, none. Sediment: a rare red blood cell leucocyte, an

occasional round cell and many squamous cells, tolerance urinalysis, normal, very slightly cloudy, acid, 1,016, albumin, none, sugar, none. Sediment same as before.

The differential count shows an increased polymorphonuclear count. Patient has a high sugar tolerance and a low systolic blood pressure.

Cutaneous tests were made and the diet arranged. In two weeks she was free from chronic depression, exhaustion, weakness and the tiredness. Systolic blood pressure, 120, diastolic, 70.

On January 29, 1929, while returning home after visiting her son at a private school, her automobile stalled in a county section and she was detained there four hours. As this was a long time after her regular hour for eating, on arriving at a roadside stand she ate some kind of cake to which she was sensitive, at about 5:00 p. m. She felt exhausted and depressed for thirty-six hours after eating this cake. After forty-eight hours she was free from all symptoms.

Later on this patient telephoned from a distant city on a Sunday morning saying that she was very weak and depressed. She felt all night on Saturday night. On being asked what foods she had eaten Saturday night that were bad for her, she said "None." On close questioning it was found that she had taken a cup of Cocomalt. Cocoa was bad for this patient. After forty-eight hours when the system had had a chance to eliminate the food to which she was sensitive, the weak, tired, exhausted, depressed condition relieved.

Following the eating of the cake the symptoms of exhaustion, weakness, depression appeared within five hours. Ten hours following the drinking of the cocomalt at night the same symptoms appeared, thus showing that the time of onset of the different symptoms is influenced by different foods.

This patient had been treated by dietitians and gastro-enterologists, but she continually grew worse under their care, and when these physicians failed to help her they told her that it was all a mental or imaginary condition. What better proof of the error of their diagnosis when all symptoms were relieved so soon after this patient avoided foods to which she was sensitive. Further proof was furnished some months later when on two different occasions the patient had eaten foods that were forbidden to her and this was followed in a few hours by a return of all the characteristic symptoms.

COMMENTS

These tired, weak, exhausted patients have a history of digestive disturbance, nervous depression and headaches in some form. These aches varied from a miserable feeling, a dull pressure, a bursting feeling, to a sharp shooting pain. Some of the headaches started in early life, while others began with the onset of their present illness. Four had headaches every day, one was confined to bed three to four days out of each week because of headaches, and all awakened each morning with headaches.

Two had cholecystectomy and appendectomy, and

the weak, tired, exhausted, depressed states are decidedly worse following these operations.

The lowest blood pressure was 87-60, the next lowest 100-70. The highest was 178-90, one was 147-90, one 138-80 while the others were between 112 and 120 systolic and 70 and 80 diastolic. After dietetic measures, all systolic pressures were between 120 and 130 and the diastolics between 70 and 75. It is interesting to note how the low blood pressures were raised and the high lowered with the treatment.

CONCLUSIONS

1. Weak, tired, exhausted, depressed states are not imaginary, nor are they neurotic in origin.

2. Patients with these symptoms are really very sick and I term their syndrome "toxic allergy."

3. A tendency to disease is hereditary, not the disease.

4. This inherited tendency may be shown in the same form or some related condition.

5. The stress and strain of life, especially if excessive, in an allergic individual, can cause severe physical and mental illness.

6. Allergy added to a weak constitution can produce insanity as shown by suicidal and homicidal tendencies in case 7.

7. What are usually called nervous breakdowns may in some cases be due to toxic allergy.

8. Cutaneous tests provide us with the means to ascertain the cause of these allergic patients.

9. Avoiding foods to which the patient is sensitive has given relief of all symptoms.

10. After relief of all symptoms, the eating of allergy foods can bring on the previous condition.

11. The return of the symptoms by the eating of the sensitive foods proves the correctness of the cutaneous tests and diet.

12. Allergy and the cutaneous tests are an important branch of medicine.

Pseudo-Cascade Stomach: Case Report*

by

DUNOVAN G. BROWNE, M.D.

and

GORDON McHARDY, M.D.

NEW ORLEANS, LOUISIANA

THE occurrence of Cascade Stomach not infrequently has gained scant mention in American literature. Its nature is little understood as is illustrated in its classification under "hour-glass" stomach to which it actually bears no definite relationship. The most comprehensive coverage on the subject is that of Lapham in 1933 which abstracts the literature accumulated since Rieder's presentation of 1910.

To create a "Cascade Stomach" the upper fundus is a flaccid posteriorly "flopped" sac devoid of peristalsis. The lower and main portion of the stomach is a normal peristaltic stomach. Characteristically the upper locus fills and the contents only cascade over into the lower portion with change in position especially upon lying on the left side.

Etiologically a transitory spasmodic type possible due to spasm of the oblique muscle of the stomach vies with an organic defect due to a gas filled splenic colon displacing an abnormally fixed or ptosed stomach or a benign or malignant intragastric deformity. There are many hypotheses which hardly deserve mention.

The symptomatology is not specific other than relief of pain by lying on the left side. There is no rationalizing the relationship to neurosis claimed by some

Physically a prominent left hypochondrium is characteristic. The diagnosis is roentgenological.

The therapy should be a conservative attempt to relieve the symptomatology by diet, sedation and antispasmodics at first. A lack of response calls for surgical intervention with the operative correction depending upon the pathology encountered. Schaffner and Burton report a lateral partial fundectomy actually resecting the upper locus; this is the only instance of such a procedure.

CASE REPORT

Case C. P. P. (T-5621). A 35 year-old white male laborer first seen April 26, 1942 complaining of post-prandial epigastric pain occurring intermittently over a period of five years. No precipitating factor could be elicited. The pain followed any ingestion immediately, there was definite quantitative dyspepsia. Relief was obtainable by lying down especially upon lying on the left side, by induced belching (effervescent alkali) and by enema. There was the sensation of food passing a constriction but no definite dysphagia. The pain had become progressive in severity provoking a ten pound weight loss. Dietary regimens and various medical therapy offered by four physicians consulted gave no relief.

Physical examination revealed an apparently normal muscular male of slender sthenic habitus. The left

*From the Department of Medicine, Tulane University School of Medicine and the Castro Enterologic Clinic of Touro Infirmary, New Orleans, Louisiana.
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Fig 1 Roentgenologic demonstration of normal gastric contour on the antero-posterior projection contrasted with a typical cascading on the lateral view when the splenic flexure was distended

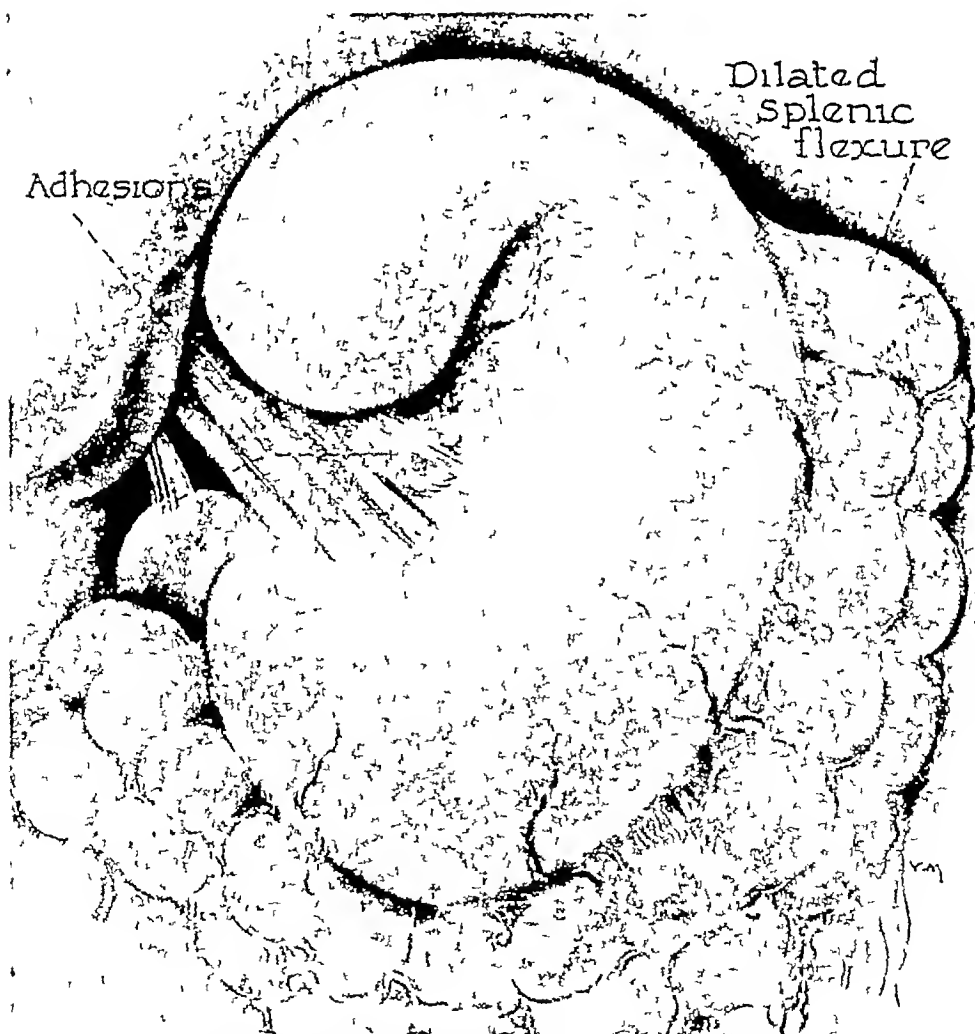


Fig 2 Artist's sketch of the gastric deformity seen at exploratory when the cardiac end of the stomach was pulled forward

hypochondrium was more prominent than the right. Proctosigmoidoscopy was negative.

Laboratory studies revealed a gastric hyperchlorhydria on three examinations, endameba histolytica and giardia lamblia in the purged stool specimen.

Gastro-intestinal roentgenographic findings (68669 and 70907) included "The cardiac portion of the stomach is markedly distorted, an upper loculus capping the distended splenic flexure—so constantly as to suggest that it may be adherent. Cascading is produced by distending the splenic flexure with air. The cecum is inverted so that its tip is directed posterolaterally. The appendix points toward and occupies the subhepatic region."

Gastroscopy revealed a large stomach. Orientation was excellent, no evidence of distortion. A fold segmented the stomach into cardiac and pyloric loculus under direct vision. A mild superficial gastritis in the cardiac loculus was the only other finding.

Effective amebicidal therapy included iodoquin and carbofene. The giardiasis was eradicated with Atabrine followed by Gentian Violet. A period of six weeks was permitted to pass, antispasmodics, sedatives, alkali and dietetic therapy were tried. There was no symptomatic response.

Admitted to Touro Infirmary June 20, 1941, an exploratory laparotomy was done by Dr. Sidney Copland. Adhesions along the lesser curvature and part of the anterior gastric simulated wall produced a short gastrohepatic ligament and fixation and relationship illustrated. The adhesions were sectioned permitting normal anatomical placement of the stomach. The adherent subhepatic appendix was removed.

The patient was relieved. Gastro-intestinal X-rays on August 20, 1941 were normal. Cascading produced previously on two occasions by distending the splenic

flexure with air was not possible at this time. When last seen on September 18, 1942, the patient was asymptomatic.

DISCUSSION

This is an excellent illustration of a so-called Cascade Stomach. It is not unlikely that the gastroscopic position of lying on the left side reduced the deformity to its minimal extent for this posture characteristically relieves discomfort incident to cascading for obvious mechanical reasons.

Production of cascading by distension of the splenic flexure supports Assmann's etiologic hypothesis; Schlenker's contention that peri-gastric adhesions are necessary for such is substantiated by the absence of the picture subsequent to release of adhesions.

We would prefer to term the Cascade Stomach due to organic deformity a pseudo-cascade stomach while that functional, spasmodic or reflex a true cascading.

CONCLUSIONS

(1) We are inclined to accept an organic background for cascading because of our findings in this and in two previous incidents. (2) Gastroscopy was not of material aid in the diagnosis. (3) Assuming that a goodly number of Cascade Stomachs are of organic origin, should conservative measure fail, exploratory laparotomy should exclude organic pathology to permit a diagnosis of spasmodic Cascade Stomach.

We are indebted to Dr. M. Teitelbaum for his cooperation in roentgenologic study.

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Pruritus Ani. A Study of Mucosal pH and Bacterial Flora. Treatment Based Upon These Findings. One Hundred Five Case Reports.

By

LEITH H. SLOCUMB, M.D.
LOS ANGELES, CALIFORNIA

PRURITUS ani is a pathological entity, the chief symptom of which is itching of the anal and perianal region. Chronicity, sameness of symptoms, lichenification, excoriation, the certainty of recurrence, all characterize the syndrome.

Text books and literature pertaining to the subject stress as important the elimination of all pathological conditions present in the area. There is no doubt that one of several complications may accompany any case of pruritus ani, but the etiology of idiopathic pruritus depends upon factors other than these local conditions.

Buie (1) aptly points out that such conditions as varicose veins, hemorrhoidal conditions, phlebitis and hypertrophied papillae accompany pruritus instead of causing it.

Davis (2) believes that pruritic changes are due to chemical and not bacterial causes, that irritating non-absorbable chemical compounds are deposited in the pruritic zone.

Tucker and Hellwig (3) are not in accord with views emphasizing bacterial and fungus infections, allergic sensitivities or neurogenic factors as the cause of pruritus ani. Their histologic studies of tissues of the anal canal do not reveal differences between pruritus patients and those not having pruritus. They report finding Meissner's tactile corpuscles beneath the tips of the anal papillae. They state that possibly inflammatory processes in the region irritate these nerve corpuscles and thus produce the sensation of itching. They also conclude that skatol may be a contributing factor in causing pruritus. Skatol is produced by decomposition of protein in the intestine. Their histologic studies of tissues of the pruritic zone coincide with those of Montgomery quoted by Buie. In a summary, Tucker and Hellwig state that their studies indicate that the underlying cause of pruritus ani is suggestive of a chemical dermatitis.

Divergent opinion as to pruritus etiology, pathology and treatment indicates that further investigation in this field of endeavor is necessary, before we arrive at the correct solution. Many causes of pruritus clear up for a time with or without treatment, but the certainty of recurrence is characteristic of the syndrome.

Normal function of the gastro-intestinal tract depends upon intricate physiological changes which include metabolic chemical and bacterial processes which are not well understood. It is evident that acid-base balance as well as a balance between absorption and

secretion are necessary if normalcy is maintained, and this may be especially true in the lower bowel. It is quite probable that the solution of the pruritic syndrome, as to etiology, lies in this direction.

In a study of colitis, Sokoloff (4) stressed the importance of acid-base balance and its relationship to bacterial flora in the lower bowel. According to Rettger, quoted by Sokoloff, cases of ulcerative and mucous colitis, showed greatly decreased or complete absence of bacillus acidophilus. With a disappearance of the aciduric flora, a shift of colonic contents to the alkaline side was constantly observed. Sokoloff quotes Laszt, that the self-disinfecting properties of the mucosa depends upon its absorptive and oxidative reducing activity, and its ability to produce an acid secretion, through the formation of lactic acid and the re-synthesis of hexose phosphoric acid, and that bacterial flora in the colon is a decisive functional factor. Sokoloff quotes Cannon and McNease, that lactose through the formation of lactic acid, creates an environmental condition favorable to bacillus acidophilus and inimical to hostile bacteria, particularly streptococci and protozoa.

The experimental work of Kendall (5) indicates that definite changes in the intestinal flora result, depending upon whether carbohydrates or proteins predominate in the ingested diet. Kendall states that at birth the intestinal contents are sterile. The first bacteria discernible make their appearance a few hours postpartum. These are adventitious organisms and so far as is known have no particular significance because the true bacteria rapidly invade the tract and supplant the first comers. These, the true and obligate nursing organisms are lactic acid bacteria. They have absolutely no putrefactive power and their existence depends upon the fact that the diet of nurslings, breast milk, contains a relatively large proportion of lactose and a small amount of nitrogenous substance, principally lactalbumin and lactoglobulin. Putrefactive products are never found under these conditions according to Kendall. And, as the infant becomes older and needs nourishment beyond maternal provision the relative reduction of carbohydrates and increase of proteins causes equivalent changes in bacterial flora. The normal carbohydophilic bacteria are replaced by such bacteria as bacillus coli, which can thrive equally well in the presence or absence of carbohydrates. Two kinds of substances may result. From carbohydrates, lactic acid is formed, but in the absence of carbohydrates, putrefactive products such as indol and

skatol are produced from proteins. The foregoing data by Kendall and others offers a tangible working basis for new fields of investigation and treatment of pruritus ani.

The purpose of this study is to ascertain whether a disturbed acid-base balance and bacterial flora are factors in producing the pathology and symptoms constantly present in pruritus ani. One hundred five cases have been studied and treated. The resulting data is shown in Tables I, II and III. Table I shows male, female and age incidence. The preponderance of males over females is excessive, as compared with published figures. It is noteworthy that age incidence is about the same for males and females. A large percentage of the series are in the age bracket between 30 and 49 years. Possibly the clinical material studied may have influenced age and sex incidence.

Table II contains 64 case reports. Data tabulated includes symptomatology, pathology and pH determinations before and after treatment, progress, recurrences and follow-up record, when it was possible to obtain it.

Table III contains 41 cases arranged as in Table II, but contains additional data which includes blood findings and a urine analysis, a Gram-negative, Gram-

positive and secretions from within the rectum. And by the usual method of toilet paper cleansing, it is impossible to rid the sulci of irritating debris and secretions from above.

Jamison (6) and later Hanes (7), and others described sub-tegumentary channels leading from the pruritic zone to the deeper tissues and possibly to the sub-mucosal region in the rectal ampulla. There is evidence, confirmatory of these findings, in this series of cases.

COMPLICATIONS EXTERNAL

In the order of frequency are skin tags, phlebitis, fissure and fistula. These complications may initiate an attack of itching or may cause exaggeration of symptoms during an attack, but chronic pruritus ani depends upon factors other than these, to explain changes of the pruritic zone, chronicity and recurrence. Gross changes of the skin of the anal canal are frequently present and appear to be an extension from the process outside and due to irritating secretions from above.

COMPLICATIONS INTERNAL

The mucosa of the rectal ampulla almost constantly shows changes from the normal and these changes may

TABLE I
Showing male, female and age incidence in one hundred five cases of pruritus ani

Age	15 Mo	20-29 yrs.	30-39 yrs.	40-49 yrs.	50-59 yrs.	60-69 yrs.	Total
Male	1	7	30	31	9	1	79
Female		5	8	10	2	1	26
Total	1	12	38	41	11	2	105

positive bacterial count in conjunction with the pH recordings. The bacterial count is made from material obtained from the rectal mucosa, cultured and stained by the Gram method.

Clinically, several interesting findings have been noted which may have to do with etiology and especially symptoms. These findings may be grouped under gross pathology and complications.

GROSS PATHOLOGY AND COMPLICATIONS

The external pruritic zone is usually characteristic in appearance. Findings depend upon chronicity, scratching, previous medication and treatment, and other forms of traumatic injury. Lichenification, varying in degree from 1 + to 4 +, wherein 1 + denotes the minimum and 4 + the maximum, is constantly present. Raised, oedematous, radiating skin folds showing excoriation and moisture are constantly present. And, constantly this moist secretion shows a pH well over on the alkaline side. Radiating skin folds are accompanied by sulci, the depth of which depend upon the thickening and oedema of the perianal skin. The summit of the skin folds is particularly vulnerable to irritations such as scratching, toilet paper, medi-

be quite marked. Redundancy and separation of the mucosa from the submucosa is a common finding. Frequently, the examining anoscope is filled with loose bulging mucous membrane, with even slight straining. Circulatory elements, both venous and lymphatic which lie between the membranes and in the rectal wall, are subject to obstruction because of lack of support and tortuosity due to these changed anatomical and pathological conditions. And, this in turn causes a disturbance of absorption and secretion of the mucous membrane and structures beneath. Hypersecretion is present in almost every case and grossly, the mucosa appears to be thickened, dull and opaque and frequently a granular, patchy, exudative inflammatory process is present. This exudative secretion constantly shows a pH, highly alkaline in reaction. The pH determinations were made with nitrazine paper, the accuracy of which seems adequate for this type of study.

Complications, at and above the linea pectinata, in the order of their frequency, include internal varicosities with varying degrees of fibrosis, cryptic dis-

The chief symptom of pruritus ani is itching of the anal and perianal regions. This symptom may be more

Consolidated record of sixty-four cases of pruritus and Correlation of symptoms and mucosal pH results of treatment

Case No	1	2	3	4	5	6	7	8	9
Sex	F	M	F	F	M	M	M	M	M
Age	75	38	39	40	27	15 mo	30	30	35
Duration Years	10	4	1 1/2	20	1 1/2	3 mo	1	1	1 1/2
Symptom severity									
Day	++	++			+	+++		-	++
Night	+++	+++	++	+++	++	+++	++		
Follows evae							++	++	
When nervous									
Pathology									
Lichenification	++	+++	+++	+++	++	+	+++	++	+
Redund mucosa	+	+	+	+			+	+	
Hypersecretion	+	+	+	+	+++	+++	+	+	
pH before treatment	8.0	8.0	7.5	8.0	8.0	8.5	8.5	8.0	7.5
Date	4-25-41	7-11-41	4-5-41	4-8-41	4-24-41	9-11-41	5-7-41	2-18-41	2-1-41
Complications									
Varicocities	+		+	+			++		+
Crypts fissure	+				+				
Progress									
Symptom free	7-10-41	10-27-41	7-24-41			10-24-41		9-15-41	3-3-41
Improved				+++	+++		++		
pH	7.0	6.0	7.5	7.0	6.5	7.0	8.0	7.0	7.0
Date				8-1-41	12-20-41		12-30-41		
Recurrence		3-3-42							
pH		8.0							
Followup									
Symptom free		5-4-42				8-20-42			2-10-42
Improved				++++	++++		++++		
pH		7.0		7.0	7.0	7.0	7.5		7.0
Date				12-10-41	5-1-42		1-11-42		

Case No	10	11	12	13	14	15	16	17	18
Sex	F	F	F	M	F	M	M	F	F
Age	41	41	45	45	48	45	42	37	46
Duration Years	2	10	20	4	20	10	1	2	8
Symptom severity									
Day		+				++	+++	++	+++
Night				+++	+++				
Follows evae		+							
When nervous	++		++						
Pathology									
Lichenification	+++	++	++	++	+++	++	+++	+	+++
Redund mucosa	++	+	+	+	++	++	+	++	+
Hypersecretion	+	+	+	+	+	+	+	+	+
pH before treatment	8.0	7.5	8.0	7.5	7.5	8.0	7.5	7.5	8.5
Date	12-12-40	10-30-41	12-24-40	3-18-41	6-25-41	5-20-41	11-17-40	2-14-42	4-2-41
Complications									
Varicocities	++	+	++	++	++	++	++	++	+
Crypts fissure		+						+	
Progress									
Symptom free	6-17-41					10-13-41		3-14-42	
Improved		+++	++	+++	+++		+++		++
pH	7.0	7.0	7.0	7.0	7.5	7.5	6.5	7.0	7.0
Date		1-22-42	3-17-41	7-16-41	11-14-41		8-25-41		9-2-41
Recurrence						12-19-41	1-26-42		2-6-42
pH						8.5	8.0		8.0
Followup									
Symptom free	5-27-42	3-16-42		2-3-42	2-10-42			3-14-42	
Improved									
pH	7.0	6.5		6.5	7.0			7.0	
Date									

Case No	19	20	21	22	23	24	25	26	27
Sex	M	M	M	M	F	M	F	F	M
Age	51	40	38	41	47	36	49	27	35
Duration Years	5 mo	15	5	1	6 mo	3	1	1	7
Symptom severity									
Day						+	++++	++	+
Night	+++	+++	+	++					
Follows evae					+				
When nervous									
Pathology									
Lichenification	++	+++	++	++	++	+++	+++	+	+
Redund mucosa	++	+	++	+	+	+	+		
Hypersecretion	+	+	+	+	+	+	+		
pH before treatment	8.0	8.5	7.0	8.0	8.0	8.0	7.5	7.5	7.5
Date	3-10-41	4-14-41	1-31-41	5-28-41	6-14-41	6-12-42	9-25-41	8-0-41	0-3-41
Complications									
Varicocities	+			+	+	+	+		
Crypts fissure				+					
Progress									
Symptom free		1-22-42	6-13-41	9-3-41		7-10-42		12-0-41	11-27-41
Improved	++				++		+++		
pH	8.0	7.0	7.0	7.0	6.5	7.0	6.5	7.0	7.0
Date	9-20-41				10-20-41		12-19-41		
Recurrence			1-5-42		3-14-42		3-2-42		
pH			8.5		9.0		8.5		
Follow up									
Symptom free	1-22-42						5-16-42	2-2-42	
Improved									
pH	6.5						7.0	7.0	
Date									

or less constant or occur only at certain times Night itching is present in all chronic idiopathic cases of pruritus ani. Symptoms vary from mild to extremely severe and often cause agonizing and sleepless nights. Marked pathology usually carries with it severe symptoms, though this is not constant.

Constipation is seldom a symptom in true pruritus ani, these cases average 2 or 3 bowel evacuations daily. And frequently, catharsis or an attack of diarrhea will initiate intense itching and cause increased pathology of the external zone.

Some cases have itching, only after a bowel evacu

TABLE II CONTINUED

Case No.	28	29	30	31	32	33	34	35	36
Sex	M	M	F	M	F	M	F	M	M
Age	50	31	28	19	35	31	30	35	39
Duration Years	15	2	1	7	3	3	3	10	6 mo.
Symptom severity									
Day	+++		+	+	++	++	++	+++	
Night		+++	++	++	++	++	++	+++	
Follows evac.									
When nervous									
Pathology									
Lichenification	++++	+++	+	+	++	++	+++	+++	+
Redund mucosa	+	++	+	+	++	++	++	++	+
Hypersecretion	+	+	+	+	+	+	+	+	+
pH before treatment	7.5	8.0	7.5	7.0	8.0	9.0	8.5	9.0	7.5
Date	4-6-42	1-28-42	10-13-41	9-20-41	7-7-41	11-23-40	11-10-41	10-24-41	11-10-40
Complications									
Varicocities		++			++		++	+++	
Crypts fissure									
Progress									
Symptom free			12-30-41	11-1-41					
Improved	++	+++			++	++	+++	+++	++
pH	7.0	7.0	6.5	7.0	7.0	7.0	7.5	6.5	7.0
Date	4-16-42	3-31-42		7-0	10-20-41	2-5-42	5-1-42	3-6-42	7-41
Recurrence			2-2-42						
pH			8.0						
Followup									
Symptom free	8-16-42		7-26-42	12-27-42	7-16-42	3-30-42		4-3-42	1-8-42
Improved		++							
pH	6.5	7.0	6.5	6.5	6.5	7.5		7.5	6.5
Date		4-24-42							
Case No.	37	38	39	40	41	42	43	44	45
Sex	M	M	M	M	F	F	F	F	M
Age	42	38	26	42	50	30	35	23	39
Duration Years	12	1 1/2	7	2	15	10	10	13 mo.	1
Symptom severity									
Day	+++		+++	++	++	+++	++	++	++
Night									
Follows evac.									
Pathology									
Lichenification	++	+	+++	++++	++	++	+++	++	+
Redund mucosa	++	+	++	++	++	++	++	++	+
Hypersecretion	++	++	++	++	++	++	++	++	++
pH before treatment	8.0	7.5	8.5	8.0	7.5	8.0	7.0	8.0	9.0
Date	6-4-41	11-11-41	7-11-41	5-1-41	10-10-41	4-14-41	2-10-42	9-20-41	2-3-41
Complications									
Varicocities	++	++	+	++	+	++	++	+	+
Crypts fissure									
Progress									
Symptom free	11-15-41	2-20-42	++	12-4-41	4-28-42	6-2-41		++	++
Improved			++						
pH	7.0	7.0	7.0	6.0	6.5	6.5	6.5	6.5	7.0
Date			11-22-41				3-15-42	2-12-42	4-23-42
Recurrence		5-29-42	12-18-41		7-14-42				5-26-42
pH		8.0	8.5		8.0				7.0
Followup									
Symptom free	11-20-41		3-28-42			3-12-42		7-2-42	
Improved		++							
pH	7.0	7.0	7.0			7.0		7.0	
Date		7-9-42							
Case No.	46	47	48	49	50	51	52	53	54
Sex	F	M	M	M	M	F	F	M	M
Age	46	32	38	38	20	32	60	41	43
Duration Years	2 mo.	8	8	2	5	1	15	2	7
Symptom severity									
Night	++	+++	++	+++	++	+++	+++	++	+
Day									
Follows evac.									
Pathology									
Lichenification	+	+++	+++	+	++	+++	+++	+	++
Redund mucosa	++	++	++	+	+	+	++	+	+
Hypersecretion	++	++	++	++	++	++	++	++	++
pH before treatment	7.5	8.0	8.0	8.0	7.5	7.5	8.5	8.0	8.5
Date	11-11-41	9-30-41	10-30-41	11-11-41	7-21-41	9-6-41	11-14-40	4-11-41	2-18-41
Complications									
Varicocities	++	++	+	+	+	+	+	++	
Crypts fissure									
Progress									
Symptom free	1-18-42	3-17-42	12-26-41	12-2-41	8-26-41	12-6-42	12-14-40	8-10-41	3-4-42
Improved									
pH	6.5	6.5	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Date									
Recurrence		4-17-42							
pH		7.0							
Followup									
Symptom free	3-14-42		1-8-42	1-8-42	7-9-42		1-25-41	1-6-42	
Improved									
pH	6.5		7.0	7.0	7.0		7.0	7.0	
Date									

TABLE II CONTINUED

Case No.	55	56	57	58	59	60	61	62	63	64
Sex	M	F	M	F	M	M	M	M	F	M
Age	53	29	21	35	66	31	42	43	29	41
Duration Years	1	2	1	6	4	4	1	7 mo	2	9
Symptom severity										
Day	++	+++	+++	+++	+	+	+	+	+	+
Night					++	++	++	+	++	++
Follows evacuation								+		
Pathology										
Lichenification	+++	++	++	+	++	+++	++	+	++	+
Redund mucosa	++	++	++	+	+	+	+	+	++	+++
Hypersecretion	+	+	+	+	+	+	+	+	+	+
pH before treatment	8.0	8.0	7.5	7.5	8.0	8.5	8.5	8.5	8.0	8.5
Date	10-16-41	11-11-41	9-28-41	11-6-41	7-8-41	4-24-41	12-17-40	7-23-41	11-11-41	10-25-41
Complications										
Varicosities	++		++	+	+	++		+	+	+++
Crypts fissure										
Progress										
Symptom free				11-21-41	8-25-41			9-16-41	1-5-42	11-16-41
Improved	++++	+++	+++			++++	+++			
pH	7.0	7.0	7.0	6.5	6.5	6.5	7.0	7.0	7.0	6.5
Date	2-16-42	2-12-41	1-27-42			12-1-41	2-17-41			
Recurrence										
pH										
Followup										
Symptom free	5-15-42		3-13-42	2-19-42	12-15-41		12-26-41	3-4-42	3-3-42	3-3-42
Improved										
pH	7.0		7.0	7.0	7.0		7.0	7.0	7.0	7.0
Date										

ation. Others are free of symptoms during the working day, but with relaxation at the end of the day, the itching begins. In all groups, perspiration exaggerates symptoms.

There has never been a satisfactory explanation as to why night itching is the outstanding characteristic symptom of pruritus ani. There is evidence in this study, that alkaline secretions from the rectal ampulla, leak out during sleep relaxation and cause irritation to the denuded pruritic zone, and thus cause the sensation of itching. The sweat glands of the anal canal probably play a part. According to Buie, the skin of the anal canal does not differ histologically, from true skin elsewhere.

TREATMENT

Treatment is directed toward correcting the high alkaline mucosal pH, constantly found in these cases, and local treatment of the ampulla mucosa and the pruritic zone.

DIET

A strict dietary regimen is most important. Those foods which tend to produce lactic acid are pushed to the limit and later regulated, depending upon pH changes. They include milk, buttermilk, acidophilus milk, lactic whey, cottage cheese, other cheeses, yogurt, beta-lactose and other carbohydrates. Those foods which produce alkalinity and putrefactive processes are eliminated from the diet, as much as possible. They include meat, leafy vegetables, citrus fruits and other foods of the kind. Hydrochloric acid, before and after meals seems of benefit in cases where bowel evacuations are too frequent and where the bowel contents are soft, sticky and acholic in appearance.

Local measures for reducing the alkalinity and cleansing the ampulla mucosa follow a lactic acid solution, containing papain, a mucous solvent is employed for this purpose. One or two ounces of a two and one-half per cent lactic acid solution, added to a pint or quart of warm water is used daily, at bedtime,

as a rectal douche. Lactic acid is more efficient than either hydrochloric acid or boric acid in maintaining a pH of between 6.5 and 7.5, and also in promoting the growth of Gram-positive bacteria.

Other local measures are aimed at correcting mucosal redundancy and separation, an almost constant finding in these cases. To correct this condition, a sclerosing agent, (5% Phenol in oil) is injected between the mucosa and submucosa. The entire area is infiltrated, often as high as three and one-half inches above the linea pectinate. The injections are made at weekly intervals, usually three injections, each time. The amount of solution used, depends upon the degree of mucosal separation. This accomplishes the same purpose as the Hanes hydrochloric acid technique for mucosal prolapse, but the procedure is entirely an office affair and in no instance have complications caused trouble.

CARE OF THE PRURITIC ZONE

Scrupulous care of the outside area is of the utmost importance. Cleansing with toilet paper is one of the main sources of traumatism. Following evacuation, the parts are carefully cleansed with castile soap and water using the hand for the purpose, and not cloth or cotton. Thorough rinsing with clear water is followed by the application of a saturated boric acid solution. The parts are patted dry and Tincture Mercuric or a like solution is painted over the itching area. Several times during the day, sponging with boric acid solution removes secretions that may have accumulated. A boric acid pack at night often gives complete relief and prevents scratching during sleep. Occasionally, mild ointments or lotions are resorted to, but usually are unnecessary.

In many of these cases a new type of suppository was used during the night. This suppository is designed in such a way that it remains within the anal canal, and it thus serves the two-fold purpose of preventing leakage of irritating secretions from above,

and of topical medication to the anal canal, the pectinate area, and the tissues of the pruritic zone outside

RESULTS

Improvement, symptomatically and pathologically, following the above outlined regimen is rapid and progressive. Some of the cases are symptom free in a few days. Other cases require several weeks before they are symptom free. As shown in Table 2 and 3, recurrences are frequent, but in every case they can be traced to failure to carry out directions as to treat-

ment. Symptomatic improvement constantly follows pathological improvement of both the mucosa and the perianal regions.

COMMENT

One hundred and five pruritus ani case reports have been tabulated and the results of treatment are shown in Tables II and III. Results in terms of improvement, pathologically and symptomatically, are in most instances, striking.

Treatment has been directed toward correcting the

TABLE III

Consolidated record of forty-one cases of pruritus ani correlation of symptoms, mucosal pH and ampulla flora

Case No	1a	2a	3a	4a	5a	6a	7a
Sex	M	M	M	M	M	M	M
Age	30	40	37	39	46	49	45
Duration years	1	10	3	10	7	25	4
Symptom severity	+++	+++	+++	+++	++	++	++
Pathology severity	+++	+++	+++	+++	++	++	++
Blood findings							
Hemoglobin %	92	90	98	92		95	95
Red Count	6200000	4960000	5100000	4710000		4800000	4910000
White Count	8600	7508	6400	9150		6300	7900
Neutrophils %	42	62	60	50		84	80
Lymphocytes %	45	23	32	32		26	33
Monocytes %	2	6	8	10		8	7
Basophiles %	1						
Eosinophiles %	10	3					
Urine	Neg	Neg	Neg	Neg		Neg	Neg
Mucosal pH	8.0	10.0	7.5	9.0	9.0	7.5	7.0
Gram Neg. Bac. %	20	15	45	25	65	75	65
Gram Pos. Bac. %			5	10	35		20
Gram Pos. Coc. %	80	85	50	65		25	10
Start treatment	2-24-42	3-1-42	3-3-42	3-24-42	10-21-41	1-22-42	1-17-42
Symptom free	—	+	+++	+++	+++	+	+
Improved			+++	+++	+++		
Date	3-10-42	4-20-42	4-5-42	4-6-42	5-4-42	4-3-42	2-11-42
pH		7.0	7.0	7.0	6.5	7.0	6.5
Gram Neg. Bac. %	50	40	60	60	5	30	80
Gram Pos. Bac. %		25	40	40	75	15	10
Gram Pos. Coc. %	50	35			10	85	10
Follow up							
Symptom free	+	+	+++			+	+
Improved			+++				
Unimproved							
Recurrence							
Date	6-9-42	5-7-42	6-26-42			7-11-42	3-30-42
Mucosal pH	7.0	7.0	7.0			7.5	7.0
Gram Neg. Bac. %	15					20	15
Gram Pos. Bac. %	75					65	70
Gram Pos. Coc. %	10					15	15

Case No	8a	9a	10a	11a	12a	13a	14a
Sex	M	M	F	M	M	M	F
Age	47	42	46	44	35	50	35
Duration years	15	1	9	10	4 mo	10	1
Symptom severity	+++	++	+++	+++	++	+++	++
Pathology severity	+++	++	+	+++	+	+++	+++
Blood findings							
Hemoglobin %	98	100	73	95		100	88
Red Count	5180000	5700000	4290000	5300000		5700000	4890000
White Count	9950	8000	7450	10800		7800	9850
Neutrophils %	50	62	60	60		65	62
Lymphocytes %	32	24	34	34		28	34
Monocytes %	10	3	6	4		6	4
Basophiles %	2	3				1	
Eosinophiles %	6	8		2			
Urine	Neg	Neg	Neg	Neg		Neg	Neg
Mucosal pH	8.5	8.0	8.5	8.0	8.0	8.0	8.0
Gram Neg. Bac. %	25	20	55	20		25	25
Gram Pos. Bac. %	75	25	5	40		25	25
Gram Pos. Coc. %		65	40	40		50	2
Start treatment	4-27-42	4-10-42	1-15-42	1-10-42	12-10-41	3-26-42	2-6-42
Symptom free	+	+	+	+	+++	++++	+
Improved							
Unimproved							
Date	5-27-42	7-31-42	2-17-42	2-22-42	2-20-42	4-30-42	3-20-42
pH	7.0	8.0	7.0	7.0	7.0	10.0	7.5
Gram Neg. Bac. %	15	20	60	75	10	60	60
Gram Pos. Bac. %	15	60			90	85	35
Gram Pos. Coc. %	10	20	50	25		5	5
Follow up							
Symptom free	+	+	+	+	+++	+	+
Improved							
Unimproved							
Recurrence							
Date	7-27-42	8-13-42	4-22-42	4-30-42	3-12-42	7-23-42	7-25-42
pH			6.5	7.5	9.0	7.0	7.0
Gram Neg. Bac. %			25	25	50		
Gram Pos. Bac. %			75	55	50		
Gram Pos. Coc. %				20	50		

high alkaline pH in the rectum and colon, and also, toward reducing mucosal prolapse and redundancy, which mechanically interferes with the free circulation of both blood and lymph of the region

There is evidence that the pathological findings which accompany pruritus ani are caused by a chemical irritant alkaline in reaction and probably metabolic in origin. There is also evidence that there is a correlation between mucosal pH and bacterial flora, alkalinity favors the growth of Gram negative bacteria,

and acidity favors the growth of Gram positive organisms

It seems probable that metabolic processes which have to do with the production of lactic acid play a most important role in maintaining normal colon physiology and that research along these lines may solve the pruritus ani problem

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TABLE III CONTINUED

Case No	15a	16a	17a	18a	19a	20a	21a
Sex	M	M	M	M	M	M	M
Age	28	27	38	44	43	45	39
Duration years	10	1	4	20	20	7	2 mo
Symptom severity	+++	++	+	+++	++++	++	+++
Pathology severity	+++	++	++	+++	++++	+++	+++
Blood findings							
Hemoglobin %	100	98	100	80	80	90	93
Red Count	5380000	4880000	5100000	5330000	4600000	4608000	5000000
White Count	7900	6200	5700	9300	5800	8200	7400
Neutrophils %	71	65	64	41	68	64	68
Lymphocytes %	24	30	26	50	26	26	26
Monocytes %	2	7	5	5	6	8	
Basophiles %	2		1	1			
Eosinophiles %	1		3	3		2	6
Urine	Neg	Neg	Neg	Neg	Alb	Neg	Neg
Mucosal pH	8.0	8.5	8.5	8.6	8.0	8.0	8.0
Gram Neg. Bac. %	40	85	98	20	25	55	95
Gram Pos. Bac. %							
Gram Pos. Coc. %	60	15	2	80	75	15	2
Start treatment	2-10-42	12-8-41	1-26-42	12-4-41	2-20-42	12-2-41	1-27-42
Symptom free			+	+		+	+
Improved	++++	++++			+++		
Unimproved							
Date	5-8-42	4-4-42	2-17-42	4-6-42	4-7-42	3-20-42	3-2-42
pH	7.0	7.0	7.0	6.5	7.5	7.0	6.5
Gram Neg. Bac. %	50	10	45	10	20	40	15
Gram Pos. Bac. %	50	10	50	00	20	10	10
Gram Pos. Coc. %		80	5		00	50	75
Follow up							
Symptom free			+			+	+
Improved	++++	++++			++++		
Unimproved							
Recurrence							
Date	5-11-42	5-4-42	6-3-42	6-16-42	7-3-42	4-18-42	4-18-42
pH	7.0	7.0	7.0	7.0	7.6	7.0	7.0
Gram Neg. Bac. %							85
Gram Pos. Bac. %							65
Gram Pos. Coc. %							

Case No	22a	23a	24a	25a	26a	27a	28a
Sex	M	M	M	M	M	M	M
Age	34	48	50	45	30	40	38
Duration years	1	10	2	30	5	25	2
Symptom severity	+++	++	++	++	++	+++	+++
Pathology severity	++	+++	+++	+	+++	+++	+
Blood findings							
Hemoglobin %	95	00	91	93	100	08	91
Red Count	5000000	4960000	4780000	4760000	5600000	5250000	4850000
White Count	9150	7800	7000	8000	12000	4400	10400
Neutrophils %	72	58	48	66	62	58	67
Lymphocytes %	24	40	40	28	34	28	28
Monocytes %	4	2	4	6	4	14	4
Basophiles							1
Eosinophiles %			8	2			
Urine	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Mucosal pH	8.0	8.5	8.0	8.0	8.5	7.5	7.5
Gram Neg. Bac. %	85	10	40	20	35	65	50
Gram Pos. Bac. %	5	70	30	60	60	10	50
Gram Pos. Coc. %	10	20	80	80	5	25	
Start treatment	1-3-42	4-30-42	1-30-42	3-2-42	4-10-42	1-8-42	11-17-41
Symptom free	+					+	
Improved		++++	++++	++++	+++		
Unimproved							
Date	4-8-42	5-18-42	3-5-42	4-22-42	5-7-42	3-27-42	1-15-42
pH	6.5	7.5	6.5	7.0	7.0	6.5	6.5
Gram Neg. Bac. %	20	40	1	1	10	2	10
Gram Pos. Bac. %	80	60	5	00	10		00
Gram Pos. Coc. %			94	9	80	98	
Follow up							
Symptom free			+		+		+
Improved				++++			
Unimproved							
Recurrence							
Date			4-18-42	4-5-42	7-21-42		2-16-42
pH			7.0	7.0	7.0		6.5
Gram Neg. Bac. %			50				
Gram Pos. Bac. %			15				
Gram Pos. Coc. %			85				

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TABLE III (Continued)

Case No.	1	2	3	4	5	6	7
Sex	M	M	M	M	M	M	M
Age	40	41	42	43	44	45	46
Duration of disease	10 yrs	11 yrs	12 yrs	13 yrs	14 yrs	15 yrs	16 yrs
Site of lesion	Perianal	Perianal	Perianal	Perianal	Perianal	Perianal	Perianal
History	Pruritus	Pruritus	Pruritus	Pruritus	Pruritus	Pruritus	Pruritus
Examination	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Diagnosis	Pruritus	Pruritus	Pruritus	Pruritus	Pruritus	Pruritus	Pruritus
Treatment	Hydrochloric acid	Hydrochloric acid	Hydrochloric acid	Hydrochloric acid	Hydrochloric acid	Hydrochloric acid	Hydrochloric acid
Results	Improved	Improved	Improved	Improved	Improved	Improved	Improved
Follow-up	10 yrs	11 yrs	12 yrs	13 yrs	14 yrs	15 yrs	16 yrs
Recurrence	No	No	No	No	No	No	No
Remarks							

The American Society for Research in Psychosomatic Problems

THIS new group which came into being in December, 1942, held an organizational meeting followed by an open session in Detroit at the Hotel Statler, May 9-11, 1943, in conjunction with the 99th Annual Meeting of the American Psychiatric Association. Under the Chairmanship of Walter L. Palmer, M.D., Chicago, Illinois, the following papers were presented, the first being read by Dr. Palmer in the absence of its author.

"Physiological Mechanisms Involved in Gastro-Intestinal Dysfunction" Donal Sheehan, M.D., New York, N. Y.

"Clinical Significance of Emotional Disturbances Affecting the Stomach, Duodenum and Biliary Tract" Dr. Sidney A. Portis, M.D., Chicago, Illinois.

"Cardiospasm: A Psychosomatic Disorder" Edward Weiss, M.D., Philadelphia, Pa.

Panel Discussion was undertaken by the following physicians: Franz Alexander, M.D., Chicago, Illinois; Beaumont S. Cornell, M.D., Fort Wayne, Indiana; George E. Daniels, M.D., New York, N. Y. and Warren S. McCulloch, M.D., Chicago, Illinois.

Dr. Sheehan's paper revealed the remarkable interest and knowledge of physiology possessed by a professor of Anatomy and emphasized particularly the now-established fact that disease, and in some instances actual pathological changes, can be the result of functional disturbances which are frequently only exaggerations of the normal fluctuations occurring in physiological mechanisms.

An autonomic response, which has been invoked in the interest of homeostatic balance or as a result of emotion may give rise to symptoms as definite as those caused by organic disease. "Functional" does not mean imaginarily. In carotid sinus syncope, in Raynaud's syndrome or in Hirschsprung's disease, the illness is obvious and real, because the functional disorder gives rise to tangible physical signs. The normal physiological balance of the body—the *homeostasis* of Cannon—gives the impression of rest, yet it is the resultant always of a thousand forces pulling in certain directions, but successfully controlled by an equal number of forces pulling in directly opposite directions. Sheehan's own work demonstrated that injury to the brain, particularly the hypothalamus, frequently results in the production of hemorrhagic ulcers in the gastro-intestinal mucosa, although the exact mechanism of this phenomenon is not known, nor is it certain that clinical peptic ulceration results from a comparable mechanism in man. The work of Wolff and his associates was cited, in which observations of the human gastric mucosa were possible through a gastric fistula. It was shown that eating, discussion of appetizing dishes and also the emotion of suppressed resentment and aggression, produced hyperemia, hyper-

motility and hypersecretion. On the other hand, the emotion of fear produced mucosal pallor, decreased motility and diminished secretion.

There is, in every organism a basic level of functional activity represented by a fluctuating base line, and every new stimulus arouses a reaction, either general or local, which must be superimposed on this base line.

Dr. Portis spoke as an internist who, though primarily interested in clinical gastro-enterology, has been convinced that the attitudes of psychosomatic medicine are today unavoidable and imperative. Both in his paper and in his reply to the discussants, he emphasized that the internist must cautiously avoid overlooking an organic lesion through division of his interest in the psychological aspects of a given case. It was no longer enough merely to conclude that a given set of symptoms were due to nervousness or agitation but it was necessary to determine the nature and sources of the anxiety, if we ever expect to do more than alleviate the functional disorder. In peptic ulcer the psychological factor now is generally admitted to a rôle of major importance in the pathogenesis, but Dr. Portis emphasized that emotional effects undoubtedly will be found to be of equal significance in producing functional over-stimulation and also atonic distention of the gall bladder. The bizarre patterns seen in the irritable duodenum should perhaps not be regarded always as due to duodenitis, but frequently as contractions and spasms resulting directly from various emotions. While the mechanisms underlying such phenomena are not too clear as yet, there is as much need to study the psyche in patients with upper right quadrant distress as in those presenting classical ulcer histories. Inevitably, then, if the internist is to accept the basic postulates of Freudianism, there is the possibility that such entities as hypertrophic gastritis might be the result of repression of oral aggression. While all this was logical, it awaited careful psychoanalysis of patients with gastroscopically proved gastritis. Dr. Portis' paper represented the furthest extent to which a careful gastro-enterologist was willing to go in the direction of psychic analysis. It proved highly stimulating and suggestive and carried the inevitable caution that our search for repressions must not befog our detection of the craters of dangerous gastric ulcers in need of surgery.

Dr. Weiss has been working in association with the Jackson Clinic and all his cases of cardiospasm have been proved not only by X-ray but also by repeated esophagoscopies. Several terms have been used to describe the condition. The pathological physiology consists in constriction at the cardia and dilatation of the esophagus above. No anatomical evidence of a sphincter muscle at the cardia has been found. The term

"achalasia" was introduced by Sir Arthur Hurst to signify "inability to relax." An associated esophagitis was attributed to the irritation of stagnant, retained food masses. The Jacksons believe that the condition is due to diaphragmatic spasm. Of 17 cases seen, 9 permitted good psychosomatic study. The disease is rare. It is also notoriously resistant to cure by drugs or psychotherapy. Dilatation by mechanical means, employing a hydrostatic or mercury dilator, is the best form of treatment. Since, in some cases, the spasm has become, for the patient, a physiological expression and solution of his mental uneasiness, the forcible use of dilatation may precipitate a definite hazard, carrying with it a suicide risk.

Two cases which were extensively studied from the psychological angle, although major analysis was not used, were reported in detail. A druggist of 55 who had had a long struggle making a living and had expected his son to come to his financial rescue, developed cardiospasm immediately on learning that his son had unexpectedly married. He said it was a "bitter pill which he could not swallow." A girl, just at puberty, developed a cardiospasm because of family disgrace brought on by the fact that her older sister became illegitimately pregnant and became also a prostitute. The phantasies and dreams of this patient revealed exultation over the idea of the sister's desired death.

Cardiospasm may occur soon after birth, at a time when ratiocination is largely absent, but as Dr Sandor Rado pointed out in the discussion, the infant, though not a rational being, is deeply influenced by the motion of oral aggression and any fear of failure to obtain food, especially if exaggerated, could give rise to a repression which might find expression in cardiospasm.

Throughout the panel discussion and the general discussion, it was emphasized again and again, that the psychic investigation of a patient is not meant to detract from every conceivable caution in the physical examination. Psychosomatic medicine has as a motto

—not less physical examination but more psychological. Although the internist feels disgrace at overlooking a physical lesion, the psychiatrist has the same concern with respect to missing an important mental fact and he also believes that this failure might be as disastrous as the other. Dr Alexander used the expression "vegetative retreat" to signify the abnormal reaction of certain individuals to threat of danger to the whole organism.

Dr Daniels felt that the reaction-pattern evoked by stimuli would depend in each case, on inherited tendencies, and the habitual focus of attention. In all cases in which emotions underlie the production of symptoms, we could never forget that the physical dynamic pattern was just as important as the psychodynamic. Dr McCulloch stressed the inconceivable complexity of physiological and psychological habit patterns and made the point that unless any given reaction-pattern was carefully related to the generality of the individual's tone, it lost its significance. He felt that collaboration between internist and analyst was desirable but that the true psychosomatic probe was something necessarily undertaken by one physician, if synthesis was to be obtained. Dr Cornell spoke of the importance of vascular spasm in ulcer production and the relation of spasm to the emotional life as conditioned by the personality and its ecological background. A further fact worth noting was that just because a patient had a repression was not proof that the repression was the cause of his symptoms. One psychoanalyst with charming frankness admitted that a patient whose headache he had attributed to a long series of unfortunate experiences, suddenly died and the post-mortem examination revealed an unsuspected glioma of the frontal lobe.

On the whole, it appeared from this meeting, that if the present high standards of papers can be maintained that the American Society for Psychosomatic Research will produce a valuable service to the entire profession. The papers will be published in an early issue of *Psychosomatic Medicine*.

Notes On Nutrition

Ophthalmology and Vitamins Vitamin A deficiency is responsible both for night blindness and xerophthalmia. There is a suggestion that there exists a form of keratitis due to lack of riboflavin. Ascorbic acid has been used in the treatment of hemorrhages in the vitreous and hemorrhagic chorioretinitis. Some ophthalmologists think that attention to the nutrition of their patients has paid dividends in increased improvement in the ocular conditions which they were treating. However, apart from Vitamin A deficiency in night blindness and xerophthalmia, this nutritional treatment of the eye is on a very unsound basis as yet.

Dietary Protein and Resistance to Infectious Dis-

eases Antibodies are globulins and possibly the liver cells, on being stimulated by an antigen, are capable of producing an altered form of globulin which is the specific antibody. Young animals, in whom the blood proteins are not as high in value as in adults, do not form antibodies as well as adults. Plasma depleted dogs are even more susceptible to infection than anemic dogs. It might be argued that during war time in a nation in which the protein content of the blood is lowered by reason of protein deficiency in the diet, that there would be an increased likelihood of infectious disease. However, in England there have been no epidemics of infectious disease in the three years

of war despite the influx of many refugees and soldiers, the migration of people within the country and the sporadic breakdown of sanitary facilities in bombed cities and towns. This may well be due to the maintenance of adequate nutrition despite the war (Am J Pub Health, 32 1319, 1942)

Recommended Dietary Allowances One of the first concerns of the Food and Nutrition Board (formerly the Committee on Food and Nutrition of the National Research Council), established in 1940 to advise on nutrition problems, was to define in accordance with newer information the recommended dietary essentials for people of different ages. Although confusion results from the great variation in standards used, it seemed advisable to attempt to derive a table of allowances which would represent the best available evidence on the amounts of the various nutritive essentials to include in practical diets. This table, while not final, is of great value.

Children, among pregnant women and ascents in Scotland, and the incidence of Vitamin deficiency is rising. Many cases of pernicious anemia in England are showing a poor response to liver therapy, and it is found that this can be overcome by simultaneous administration of ascorbic acid. In an orthopedic service in England during 1941-42, a 50 per cent increase in the number of cases of rickets was seen, and a 15 per cent increase in acute rickets, this being of a more severe type than formerly seen. Many cases were in babies breast fed from mothers receiving no Vitamin D. These findings are of importance to us in America, as suggesting the kind of results we may later encounter, should our food supplies be too seriously affected by the war (Lancet, II 278, 1942), (Brit Med J, II 440, 1942)

Diet and Gastric Lesions Since Fibiger first succeeded in producing lesions in the forestomach of rats by infecting them with the parasite *Gonyzylonema neoplasticum*, many thought the results were not due to the parasites but to the bread and water diet which his rats were fed, and this has led to a long list of experiments in which various sorts of diets were used in the attempt to produce gastric lesions. Vitamin A starvation, protein deficiency and high fat diets are a few of the conditions which have been found to produce gastric lesions in the rat. Diets involving the irritant, kieselguhr, also have produced gastric lesions.

The safest way to insure that the dietary allowances are met is to include certain foods in the diet daily in specified amounts. One dietary pattern which contains a variety of foods commonly available is given here-with

	List I
Milk	1 pint
Egg	1 daily, if possible (On days not used, beans, peanuts, cheese or more milk or meat to be used instead)
Meat, fish or fowl	1 or more servings
Potato	1 or more
Vegetables	2 or more servings One green or yellow
Fruits	2 or more One citrus fruit or tomato or other good source of Vitamin C
Cereals and bread	Whole-grain or enriched
Other foods as needed to complete the meals	

normal diet, showed that the absence of Vitamin A in the diet over months did not increase their fatigue or ability to work. However, they were given high amounts of Vitamin A before the experiment began, and the stored vitamin obviously explains the interesting fact that they all maintained normal blood values of Vitamin A throughout the period of several months. This shows that if one has a good supply stored in the liver, he will not suffer much should he fail to take a daily dose of Vitamin A (Am J Physiol, 137 551, 1942)

The Protein Value of Soybeans, Peanuts and Cottonseed Due to the scarcity of meat and milk, two of our best sources of good protein, we must try to find adequate cereal and vegetable proteins to take their place, especially in the lower income groups. Preliminary work has shown that peanuts, soybeans and cottonseed contain very valuable proteins which, when added to wheat flour, greatly increase the growth rate of animals fed on it. This may be due to the fact that the growth stimulating amino-acid, lysine, is present in greater amounts in the proteins of soybeans and peanuts than in the protein of wheat. It is suggested that the experiments with these two products be continued as offering perhaps the best source of non-animal protein for periods when meat and milk are scarce in the civilian diet.

Letters

NUTRITIONAL VERSUS PSYCHIC FACTORS IN PEPTIC ULCER

To the Editor

Early reports from Europe suggested that the incidence of peptic ulcer was increased as a result of war-induced anxiety states and this led me to report the

observation of an increase in my gastric acidity as a result of a fear of being shot in 1928 (Amer J Digest Dis, 9 188, 1942). Recently, however, Laird reported that some internees who had suffered from stomach ulcer and had been on special diets fared well after being confined in a Japanese internment camp.

(Nutrition Reviews, 1 97, 1943) It hardly seems likely that these internees fared well because of a decrease in anxiety after being interned by the Japanese and the results suggest that nutrition is more important than psychic factors in determining the course of peptic ulcer

Before the reports of presumably war-increased peptic ulcer came to my attention, I doubted whether a psychogenic increase in gastric acidity such as I observed in 1928 would be likely to give rise to peptic ulcer I doubted this because the increase in my gastric acidity at that time did not give rise to any noticeable sensation although similar increases in my gastric acidity, which were produced under more normal psychologic conditions by restricting my protein intake (Amer J Physiol, 77 166, 1926), gave rise to an increased desire to eat or to a heartburn-like sensation in the gastric region (Arch Int Med, 39 710, 1927) It therefore seemed that the emotional disturbance which increased my gastric acidity in 1928 also increased the defenses against peptic irritation or erosion If, for instance, psychic factors which increase gastric acidity simultaneously increase the pancreatic secretion, this would at least serve to neutralize an increase in the acid contents reaching the duodenal region The apparent increase in peptic ulcer

in the European war zone may therefore have been due more directly to disturbances in nutrition than to anxiety induced by fear, etc.

The report of Laird seemed to imply that a diet high in carbohydrates such as was supplied in the Japanese internment camp might be beneficial in peptic ulcer cases However, the diet was incidentally inadequate in total calories and undernutrition evidently explains why the ulcer cases fared well My observations showed that gastric acidity was reduced by undernutrition and increased when the total calorie intake was increased by increasing the carbohydrate intake (Amer J Digest Dis, 10 121, 1943) Similarly, a peptic ulcer regimen of "part-time daily fasting," such as is advocated by Campiche (Amer J Digest Dis, 10 197, 1943), would, on the basis of my studies, be expected to reduce the fasting gastric acidity at least part of the time and particularly in older individuals or in those with lowered reserves. In any case, more reports like that of Laird would help to settle the question of the relative importance of nutritional and psychic factors in peptic ulcer

Frederick Hoelzel,
Department of Physiology,
University of Chicago

Editorials

THE DIFFERENTIATION OF INTRAHEPATIC AND EXTRAHEPATIC JAUNDICE

BECAUSE the differentiation of intrahepatic and extrahepatic jaundice is often a difficult problem for the gastro-enterologist, he will always be scanning the literature for every bit of help In the August, 1941 issue of the Archives of Internal Medicine, Lord and Andrus reported excellent results with the intramuscular injection of Menadione (Vitamin K) which has an effect on the plasma prothrombin In a series of cases, they felt that the test was almost uniformly accurate

In the test, the initial level of plasma prothrombin is determined on two successive days and if the two levels are within 5 per cent of each other, 2 mg of Menadione is injected intramuscularly and the prothrombin is determined at intervals of twenty-four, forty-eight and seventy-two hours On the other hand, if there is a difference greater than 5 per cent in the two initial levels of prothrombin, the level is determined on the third day and so on until the levels on two successive days are found to be within 5 per cent of each other When such agreement occurs, the Menadione is administered

At the end of twenty-four hours a second sample of blood is examined, and if a rise of 10 per cent or more in the plasma prothrombin has occurred, the patient is considered to have extrahepatic jaundice and no further determinations are made On the other hand, if a rise of less than 10 per cent occurs, it is necessary

to determine the plasma prothrombin level at either forty-eight or seventy-two hours after the injection. If the rise is then 15 per cent or more over the initial level, the patient probably has extrahepatic jaundice if less than 15 per cent, the jaundice may be considered to be of intrahepatic origin and associated with definite damage to the liver

Finally, in the interpretation of the test the authors have observed that every case of jaundice in which the initial level of plasma prothrombin was 80 per cent or more has been one of extrahepatic jaundice

TISSUE CHANGES IN VITAMIN DEFICIENCIES

FOR the student of dietetics who wishes to know what really happens to the tissues when certain vitamins are lacking in the diet, the article by Wolbach and Bessey in the July, 1942 number of Physiological Reviews can be highly recommended They point out, for example, that ascorbic acid is necessary for the formation of collagen Vitamin A is necessary for the functions of various epithelia though not for their growth and survival In some unknown way it is responsible also for the growth of bone, and it is closely related chemically to the visual purple Vitamin E is necessary for the metabolism of skeletal muscle and for the survival of embryonic tissues Interesting are the relations between Vitamin B and the physiology of the skin, the nerves and the digestive tract

Another excellent review of the present-day status

of our knowledge about vitamins is by Hugh Butt and Russell Wilder and is published in the February, 1942 number of the Archives of Internal Medicine. According to them, Vitamin A is apparently concerned with the structure of growing bone. The liver has a great deal to do with the metabolism of Vitamin A. As one might expect, among the healthy Javanese the output of thiamine is considerably lower than the average found in this country. Perhaps with a low intake throughout life, the body of the Oriental learns to get along with but little B₁.

Butt reports that as yet there is no laboratory procedure for the diagnosis of pellagra. It is highly desirable that simple laboratory tests be worked out which will enable a physician to tell definitely whether or not a given patient needs an extra supply of any particular vitamin.

Interesting is the fact that recent studies indicate that the earliest symptoms of deficiency in riboflavin are burning and itching of the eyes, photophobia, lacrimation, rapid visual fatigue, poor vision and inability to see distinctly in dim light.

An interesting statement made by Butt is that there is no evidence as yet that pantothenic acid is of value in medicine. Vitamin C appears now to have much to do with the metabolism of aromatic amino acids in the growing human organism. Interestingly, so-called sub-clinical scurvy levels of less than 0.4 mg. of C per 100 cc. of plasma are found so commonly among healthy

persons that such measurements cannot be used any longer for the diagnosis of disease. Vitamin D apparently exerts its anti-rachitic properties through its ability to increase the phosphate in the serum. Most of the work done on the giving of Vitamin E to patients with muscular dystrophies has been disappointing. It is now hard to explain the good results at first reported by some men.

WHY DOES A PATIENT HAVE A CHILL?

ONE of the greatest needs in medicine today, after 2,000 years of clinical observation, is a careful study of the mechanism and significance of common symptoms. For this reason, it is particularly gratifying to read a paper by George A. Perara in the August, 1941 number of the Archives of Internal Medicine on what can be learned about chills. Why do they come when they do, how are they produced, and what happens at the time to the heart rate, respiration, blood pressure, et cetera? What happens to the blood count and to the several known constituents of the blood? What goes wrong with the mechanism of temperature regulation? What is the purpose of the chill, in other words, what is the body trying to do? Where is the center from which the "storm" emanates? Can a sympathectomized limb take part in a chill? These and many other questions are answered, as far as is now possible, in this interesting article.

Abstracts of Current Literature

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CLINICAL MEDICINE

STOMACH

RAVEN, R. W. *Inoperable Gastric Cancer Treated with Radon Seeds. Lancet, 243 335, Sept., 1942.*

During the years 1936-1941 inclusive, the author treated 34 patients suffering from inoperable cancer of the stomach with radon seeds. The author describes the following technique for interstitial irradiation: "After surgical exposure, the size and shape of the neoplasm is carefully measured and from graphical data the amount of radon required is estimated by the physicist in attendance at the operation, who will also indicate the most appropriate theoretical sites for the implantation of the radon seeds. Souttar's radon-seed introducer is pushed obliquely through an area of normal stomach wall near the lesion and radon seeds are inserted around the growing edge of the carcinoma. Seeds are also inserted uniformly throughout the body of the tumor one cm. apart. It is necessary

to reinsert the radon-seed introducer through different points in the stomach wall in order to reach the various areas of the tumor. For growths approximately 12 cm. by 10 cm. in size, 30 radon seeds of two milluries each are required to secure uniform irradiation when the radon seeds have been inserted, the abdomen is closed in layers without drainage. A plain X-ray picture is taken of the stomach as soon as possible to determine the position of the radon seeds."

The author emphasizes that radon-seed irradiation of the stomach is attended by greater dangers than is the case with the breast, mouth and cervix uteri. Radiation sickness is common. A fever may develop. A secondary anemia and sometimes marked leucopenia may follow. Leakage of the stomach contents through the puncture holes made by the radon-seed introducers may give rise to peritonitis. Radio necrosis with sloughing of the neoplasm and hemorrhage or perforation may develop immediately or several weeks later.

The results in the treatment of the 34 patients by the method described above are as follows 1 Two are still alive (one 3 years and one 7 months after treatment) Three of the whole series survived for more than a year, 14 survived between 4 and 9 months, and 17 died within 3 months of treatment 2 The method prolongs life and ameliorates symptoms in many patients—David J Sandweiss

DILLON, J G *The Respiratory Function of the Digestive Tract as the Basis of Roentgenographic Life Test* *Am J Roent Rad Therapy*, 48 613, Nov, 1942

The mechanism of the entrance of air into the stomach is still uncertain according to Dillon He believes that air enters the stomach by suction during inspiration In order that air may enter the esophagus on inspiration a negative pressure in the esophagus during inspiration is necessary, which he believes actually occurs Entry of air into the stomach during inspiration necessitates a negative pressure in the stomach He mentions that in cases of paralysis of the diaphragm, there is a greater accumulation of air in the stomach A discussion of the presence of air in the gastro-intestinal tract is presented in detail, particularly the absence of air in the tract in still-born fetuses, because of absence of respiratory movements, the presence of air in the stomach in cases of atresia of the esophagus with fistula, and the absence of air without the fistulous communication—Maurice Feldman

GOLDING, F C *The Association of Atrophic Gastritis with Hypothyroidism, Preliminary Report of Eleven Cases* *Ann Int Med*, 17 828, Nov, 1942

This is a study of a series of hypothyroid patients to determine if there be a significant proportion also having gastric atrophy Eleven case reports accumulated in the Colorado General Hospital and its Out-Patient Clinic are analyzed Gastroscopic and laboratory studies of the stomach of such patients was done Atrophy of the gastric mucosa was found in 10 cases The likelihood of error in gastroscopic studies was to some extent obviated by having the studies checked by 1 or more additional observers, and in 2 cases the study was done more than once In only 1 case was biopsy study done Achlorhydria was found in 3 and a normal acid value found in 2 Since two-thirds of the cases had gastro-intestinal symptoms, the question whether gastric atrophy was an independent and coincidental disease is discussed The basal metabolic rate was negative in all cases, all went as low as minus 19, and 3 were less than minus 40 Of the four cases classified as true myxedemas there were 3 having no gastro-intestinal symptoms

Several hypotheses are discussed, tending to explain why gastric atrophy should occur with hypothyroidism The simplest one, reasoning that slowing the metabolic activity decreases the activity and cell replacement of the gastric glands, appears tenable, another hypothesis, concerning a myelotrophic hormone of thyroid origin, and a third, the concept that atrophy of the gastric mucosa may be due to a deficiency of a gastropic hormone, are also presented—Virgil E Simpson

DUDLEY G S, MISCALL, L AND MORSE, S F *Benign Tumors of the Stomach* *Arch Surg*, 45 702, Nov, 1942

Certain facts make it important that the physician have more than an academic knowledge of the benign gastric tumor The reasons given by Dudley, Miscall and Morse are as follows (1) The reported clinical rarity is surely relative and may be due to lack of recognition (2) Errors in diagnosis have often led to unnecessarily radical operations (3) Serious illness may result from strangulation, pyloric obstruction or hemorrhage (4) Malignant degeneration often is a result 108 cases of benign gastric tumor were studied Of these 76 of the lesions were demonstrated at autopsy and 32 at operation Most of them were not accurately diagnosed before death or operation for various reasons In many cases the patient remained almost asymptomatic Others had such complex and alarming symptoms that diagnosis was difficult, the condition may be confused with gastric carcinoma or bleeding peptic ulcer Pyloric obstruction and hemorrhage are the most common complaints requiring treatment in benign tumors, and since, on roentgen examination, they appear similar to gastric cancer and peptic ulcer, numerous diagnostic errors are made Surgical treatment of benign gastric tumors is justified in view of the dangers of hemorrhage and malignant degeneration Local incision is enough, as a rule, except for the sessile adenomatous polyps at the pylorus, in which case gastric resection is probably indicated—Francis Murphy

BOWEL

MILLER, E R AND HERRMANN, W W *Argentaffin Tumors of the Small Bowel A Roentgen Sign of Malignant Change* *Radiol*, 39 214, Aug, 1942

Carcinoids or argentaffinomas are rare tumors originating in the argentaffin cells situated at the bases of the crypts of Lieberkühn in the gastro-intestinal tract They are usually benign and of no clinical significance On the basis of their affinity for silver, the tumors have been designated argentaffinomas The primary lesions do not enlarge greatly toward the lumen but remain chiefly in the submucosa When malignancy supervenes, the tumor invades the wall of the bowel and extends into the mesentery It may spread over the peritoneum Kinking or knuckling of the bowel occurs at the site of the lesion This seems to be due to the contraction and growth of the fibrous stroma of that portion of the tumor that has invaded the mesentery This characteristic of argentaffin tumors facilitates radiological diagnosis

In the typical case the patient is middle-aged and complains of long-standing gaseous distention, bloating, periumbilical pain, and steadily increasing loss of weight Occasionally he has diarrhea and he may have rumbling or rushes in the abdomen The clinical picture is one of chronic and increasing partial obstruction of the small bowel The distention is usually so great that no tumor is palpable The guaiac test for blood in the stool is usually negative since the tumors do not ulcerate or bleed Roentgenologically the small bowel is seen to be distended with gas and fluid up to a point of partial obstruction On careful examination at the site of obstruction, a small filling defect can be found and the bowel is seen to be kinked. Since the primary lesion is usually small the obstruction

tion is due to knuckling of the bowel and not to the tumor. It is the coexistence of kinking and tumor of the bowel which suggests the diagnosis. Other small-bowel tumors such as polyps, lipoma, and carcinoma, produce obstruction because of intraluminal growth of the lesion or intussusception of the bowel.—Fianz Lust

PAGE R. C., BERCOVITZ, Z. AND DE BEER, E. J. *A Comparative Study of Dextrose and Dextrin Tolerance in Patients with Chronic Ulcerative Colitis*. *J. Lab. Clin. Med.*, 28:66, Oct., 1942.

Oral dextrose and oral dextrin tolerance tests were performed on 23 cases of chronic ulcerative colitis. The dextrin was a mixture of dextrans and maltose. The blood sugar after the dextrose administration rose 42% above the fasting level at the end of 1 hour, 7% in 2 hours, and 10% at the end of 3 hours. With the dextrin test, the blood sugar rose 70% above the fasting level in 1 hour, 21% in 2 hours, and 6% at the end of 3 hours. The conclusion is that dextrin is better absorbed from the intestines in chronic ulcerative colitis than is dextrose.—Philip Levitsky

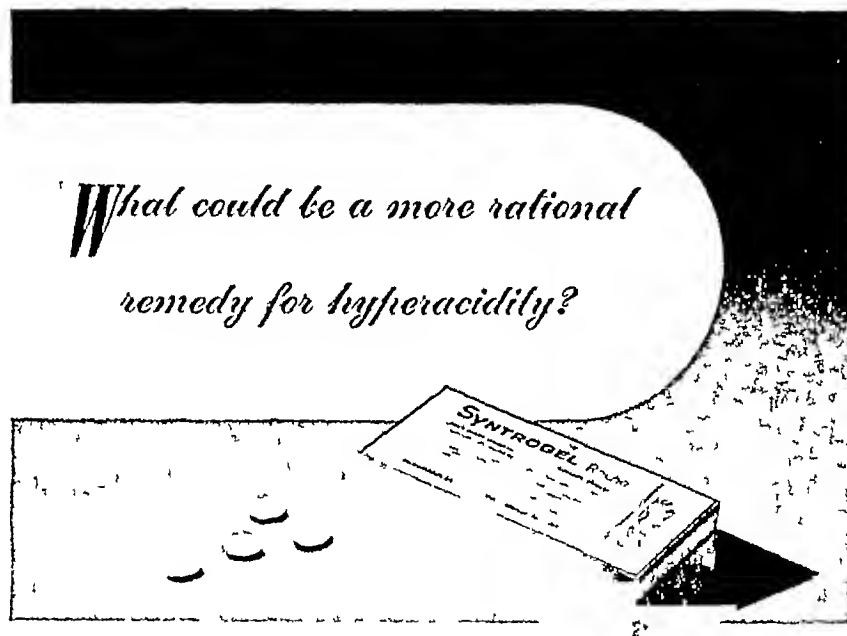
ELSON, K. A., CHORNOCK, F. W. AND DICKEY, F. G. *Intubation Studies of the Human Small Intestine XXIII. A Method of Determining Digestive Activity in Any Portion of the Gastro-Intestinal Tract, with Some Measurements of Protein Digestion in the Stomach and Small Intestine*. *J. Clin. Invest.*, 21:795, Nov., 1942.

Elsom, Chornock and Dickey have devised a method for measuring the digestion of solid food substances in any part of the human gastro-intestinal tract. The substance to be tested is placed in a fenestrated metal cylinder which is housed inside a second cylinder for protection of the contained material from the digestive juices. The apparatus is introduced by intubation to any desired portion of the gastro-intestinal tract. At the time desired the fenestrated cylinder is partially ejected from its housing by air pressure, so that the test substance is exposed to the digestive juice. The amount of material lost by digestion in a measured period of time is determined chemically. Data are presented on the digestion of pork heart

muscle after three hours. Individual observations were made on the stomachs of 10 normal persons and 10 with achlorhydria; multiple observations were made at different levels of the small intestine of two normal subjects. The average digestion was 53% in the normal, 23% in the acid free stomach, 45% in the normal duodenum, 41% in the jejunum, 42% in the ileum. Digestion appeared practically unimpaired when all intestinal contents proximal to the area being studied were removed by tube, but seemed moderately impaired when preliminary lavage removed all the contents of the area being studied.—Edgar Waybarn

BERGER, L. AND KOPPELMAN, H. *Primary Carcinoma of the Duodenum*. *Ann. Surg.*, 116:738, Nov. 1942.

Primary carcinoma of the duodenum is reported to occur in from one case in 3,000 to one in 31,000 autopsies. This is a small incidence, but the condition should be considered as a clinical possibility rather than be rejected as too remote for clinical consideration. The authors report a case of a 53-year-old man who had constipation, anorexia, loss of weight and a severe pain in the right side of the abdomen, radiating to the back and occasionally relieved by food. A G.I. series revealed an irregular



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duodenal cap and irregularity of the caecum suspicious of carcinoma. Cellotomy revealed abdominal carcinomatosis, but no source of primary tumor. The patient died of an acute coronary occlusion on the 12th post-operative day and autopsy revealed a primary cancer of the infrapapillary portion of the duodenum. The authors then go on to give an extensive review of the literature on primary carcinoma of the duodenum, incidence of the lesion in the various anatomical portions of the duodenum, operative procedures and mortality statistics following surgery. Interestingly enough the primary lesion in this case was shown on the X-ray films but was overlooked until the films were reviewed following the post-mortem examination.—Frank Neuwell

HERRIN, J. O., GLASER, S. T. AND LANG, K. *New Methods for Determining the Viability of Bowel*. Arch Surg 45 785, Nov. 1942

So far no method has been devised by which to determine whether or not the circulation in the bowel will be reestablished after a strangulated hernia is released. It is, however, most important to decide quickly and accurately on the viability of the bowel. Methods suggested are the use of fluorescein procaine hydrochloride used locally, and inhalation of pure oxygen. A fluorescein test is presented here which makes immediately available direct visual evidence of the viability of the injured part of the intestine. Procaine hydrochloride injected along the vessels leading to a strangulated loop of intestine releases vascular and muscular spasms, thus restoring the viability of the intestine. This method acts not only as a diagnostic agent but as a therapeutic measure. According to animal experimentation and clinical evidence, the time of strangulation is most important for the return of circulation to the damaged bowel. Persistence of the contraction should not be considered as proof of nonviability.—Francis Murphy

GINZBURG, L. AND GARLOCK, J. H. *Regional Ileitis*. Ann Surg, 116 906, Dec., 1942

This article is a critical review of the disease commonly termed

regional ileitis after 10 years of study of the condition and of patients who had undergone various operative procedures for the disease. The authors first emphasize that when the disease process is localized to an area within the last 4-5 feet of the terminal ileum and no other part of the small intestine has any involvement, the procedure of choice is ileocolostomy with exclusion of the involved segment rather than resection as was formerly advocated. However in case laparotomy reveals multiple and separate areas of involvement of the small intestine, the condition is considered as a non-surgical disease. Resection is no longer advocated for localized distal ileitis because experience has shown that a short circulating operation is sufficient to permit healing of the bowel, closure of fistulas, sinus tracts, etc. The operative risk is less in case of ileocolostomy; no deaths in 51 exclusion operations whereas 4 deaths occurred in 21 cases of ileocolic resection. The clinical picture of distal ileitis is discussed briefly and it is emphasized that genito-urinary and gynecological symptoms may result in inflammatory fixation of diseased small bowel to adjacent structures. The appendix should be left in situ when distal ileitis has been responsible for symptoms simulating acute appendicitis, in fact, unless perforations are present the abdomen should be closed since spontaneous remissions of the ileitis are common and may last for years.—Frank Neuwell

LIVER AND GALL BLADDER

HEFLER, O. F. AND GURLEY, H. *The Normal Value for the Hippuric Acid Liver Function Test*. J Lab Clin Med 27 1593 Sept 1942

The authors found that the addition of ammonium sulphate to the urine in order to decrease the solubility of the hippuric acid rendered the test more accurate and consistent. They found the lower limit of normal to be 90%. No upper limit was established because of the correlation between excretion and body weight.—Philip Levitsky

LOWRY, J. V. ASHBURN, I. L., DAFT, F. S. AND SEBRELL, W. E. *Effect of Alcohol in Experimental Liver Cirrhosis*. Quart J Studies Alcohol 3 2, Sept., 1942

The authors, recognizing the con-

sistent production of liver cirrhosis by means of a deficient diet carried out experiments to observe the effects of the substitution of alcohol for drinking water on the amount or degree of cirrhosis produced in a given length of time. Paired litter mate Albino rats were used in the experiments. The diet used was the low-protein low-cholesterol diet which has been reported by Daft, Sebrell and Libbe to produce liver cirrhosis in rats consistently. Twenty-one pairs of rats were allowed to eat the diet ad libitum, one rat of each pair was allowed water for drinking, the other one drank 20 per cent alcohol. In 11 of the 21 pairs the liver cirrhosis was of definitely greater degree in the ones drinking alcohol. In 1 pair, the rat drinking water had a greater degree of cirrhosis. In 7 pairs the cirrhosis was of about equal degree, and in 2 pairs, sacrificed after 28 and 49 days respectively, no cirrhotic changes were observed. In a second experiment 16 pairs of rats were fed an equal amount of the diet, in order to rule out an effect of a varying food intake, with the addition of water and of alcohol as before. All the rats with the exception of one pair, which drank alcohol, had a noticeable increase in hepatic cirrhosis over the water drinking mates. Some of the cirrhotic lesions were markedly increased others less so, but in the liver of the one that drank water, which showed an increased liver change, the difference was slight.

Fatty changes in the liver always preceded the development of the cirrhosis in all of the rats. There seemed to be no doubt that alcohol increased the severity of the cirrhosis but the mechanism of the effect is not clear. It may involve a more complex mechanism than direct toxicity. That the liver cirrhosis may be a result of the perversion of fat metabolism due to a dietary deficiency is suggested by the apparent effectiveness of choline and substances with a choline-like action in preventing the fatty and cirrhotic changes in the liver. The relationship of alcohol metabolism to fat metabolism in rats is indicated by the reports (Emerson et al, Mitchell), that the deposition of body fat or a fat like substance follows the ingestion of alcohol.—N. W. Jones

The Newer Concepts of Meat in Nutrition

Meat... *and the Acid-Ash Diet*

MAINTENANCE of urinary pH within certain limits is frequently advisable in the treatment of local conditions in the urinary tract. This may be accomplished by the administration of inorganic salts and by the institution of proper diet. In some cases both means are utilized, while in others diet alone may suffice.

A diet adequate for this purpose must be so organized in pH influencing factors that the urine will show the desired hydrogen ion concentration. Thus dietary adjustment becomes a valuable tool in the treatment of urinary tract affections.

Phosphatoptosis, with or without calculi formation, and infection with *Escherichia coli* are common

conditions of the urinary tract in which maintenance of an acid pH of the urine is indicated. Because phosphate precipitates only in an alkaline medium, phosphatoptosis and the recurrence of phosphate concretions are prevented by holding the urine to an acid pH. Since an acid urine also is unfavorable to the growth of *Escherichia coli*, an acid-ash diet becomes an important instrument in therapy.

Meat is a good source of acid forming elements—chlorine, phosphorus, and sulfur. Hence it is an important constituent of the acid ash diet. In addition, it provides the patient with biologically adequate proteins, B vitamins, and the essential minerals iron and copper.



The Seal of Acceptance denotes that the statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
CHICAGO

TAYLOR, W B *Internal Biliary Fistulae Can Med Ass'n. J.* 47 332 Oct, 1942

Fistulous communications between the gall bladder or the bile ducts and an adjacent viscus is a relatively rare finding. Since the use of the X-ray, the condition has been more or less stumbled upon periodically. This article reports on five cases representing all the cases of internal biliary fistulae diagnosed in the last five years in the Montreal General Hospital. Prior to that time there were no cases with such a diagnosis.

The common cause of an internal biliary fistula is the presence of biliary calculi. The largest number of fistulae occur between the gall bladder and the duodenum or the colon or between the bile passages and the stomach, the duodenum or the external abdominal wall. Courvoisier stated that biliary fistulae, of some variety, occur in 26 per cent of autopsies in which gall stones are found. Fistulae have been reported as the result of foreign bodies lodged in the biliary system. They may be secondary to a liver abscess, a hydatid cyst or to the invasion and necrosis of a neoplasm from an adjacent viscus. They may have their basis in a gastric or a duodenal ulcer. Rarely, biliary fistulae may be caused by trauma. Altogether, the most common cause is the presence of stones. Gall stones and fistulae are more frequent in obese women. There are two types of gall stones: metabolic and infective. The former are usually single, symptomless and are composed of cholesterol whereas the latter are multiple and contain a nucleus or organic material. Ulceration of the gall bladder wall is usually due to stones of the metabolic type. This ulceration may result in the direct formation of a fistula or of an abscess. The immediate dangers associated with internal biliary fistula formation are hemorrhage and internal obstruction. The author discusses quite fully the pathogenesis of fistulae and gives the symptoms and diagnosis along with a description of six cases.—Ira A. Manville

LESLIE, A *A Simplified Bed-side Test for Latent Jaundice J Lab Clin Med.* 28 6, Oct, 1942

The "triple response" of Lewis is produced in the arm, by means of an ordinary rubber band. When

the wheal appears, a glass slide is pressed over it to blanch the surrounding skin. In the presence of latent jaundice, the wheal has a definite yellow color.—Philip Levitsky

RITVO, M AND RITVO, M *A Substitute for the Fatty Meal in Cholecystography Am J Roent Rad Therapy*, 48 632, Nov, 1942

Ritvo and Ritvo describe a means of eliminating the usual fatty meal utilized in cholecystography. The foods most commonly used to accomplish the purpose of contracting and emptying the gall bladder are cream, eggs and butter, which are the most efficient substances. They note the objectionable features of the usual fatty meal of eggs and cream as follows: (1) it causes some individuals to suffer from bloating, nausea and vomiting, (2) persons rebel against partaking of a large breakfast, (3) many patients have an aversion for eggs, cream and butter, (4) it interferes with further gastro-intestinal studies simultaneous with cholecystography. They found, as has previously been pointed out, that a mixture of 45 per cent egg-yolk and 10 per cent lecithin will give a good response as well as eliminate the objectionable features mentioned.—Maurice Feldman

CLUTE, H M AND LAWRENCE, K B *Cholangiographic Artefacts Resembling Common-Duct Stones New Eng J Med*, 227 727 Nov, 1942

After operations for gall stones a stone may be left in the common duct and may be overlooked at the opening of the common duct. To avoid this trouble, visualization of the common bile duct by the injection of radiopaque substance through the T tube and the taking of quick X-ray films has been developed in recent years. Such post-operative cholangiograms have proved to be highly reliable. However, artefacts occur. Four such cases are described. Clots of old blood, bile and mucus clinging to the lower end of the T tube or air bubbles may be the cause of such artefacts.—Rudolf Schindler

LAWRENCE, K. B AND CLUTE, H M *Intrinsic Diseases of the Liver Simulating Acute Cholecystitis New Eng J Med*, 227 701 Nov, 1942

Several cases of intrinsic liver diseases are reported which simulated acute cholecystitis so closely that the diagnosis was often difficult. In 3 cases acute cholecystitis was simulated by carcinoma of the liver. In the 4th case acute hepatic necrosis was the cause of the symptoms.—Rudolf Schindler

COHN, C *Sodium D-Lactate Tolerance as a Test of Hepatic Function Arch Int Med* 70 829, Nov, 1942

The use of intravenously injected sodium d-lactate as a test for liver function followed studies on normal persons and on patients with acute diffuse hepatic parenchymal injury. When compared with other procedures, the sodium d-lactate tolerance test proved to be most helpful in differentiating jaundice due to extrahepatic biliary obstruction and jaundice due to hepatic parenchymal damage. The present paper deals with further studies on the use of this agent as a differential diagnostic test, and is based on the ability of normally functioning hepatic cells to convert blood d-lactate into glycogen. The dextro-rotatory form of lactic acid is the physiologically occurring isomer which is encountered as an intermediary in the carbohydrate cycle involving muscle and liver. The test consists of injecting intravenously in a fasting patient, 75 mg per kg of body weight of sodium d-lactate as a 12-14 per cent solution. A control sample of blood is taken before injection and another specimen 30 minutes later. With this method, normally functioning hepatic parenchymal cells are capable of removing all or almost all of the injected lactate within 30 minutes. The retention of 5 mg per 100 cc or more of the injected lactate above the control level after a half hour is regarded as indicating hepatocellular injury.

Results obtained with this test on 63 patients with jaundice are presented. Of 36 patients with jaundice due to diffuse hepatic parenchymal injury, 34 showed an abnormal retention of injected lactate. In 4 of 24 patients with jaundice due to extrahepatic biliary obstruction, there was an abnormal retention of injected lactate. Biopsy at operation or necropsy showed considerable associated injury to the hepatic cells in 3 of these 4 cases. Comparative studies were

The Effect of Atropine on the Gastro-Intestinal Canal and its Glands*

By

V E HENDERSON, M B †

and

M O SWEETEN, B Sc

TORONTO CANADA

WHEN the Editor asked for a review on Atropine and Belladonna, it seemed opportune to clarify certain conceptions which stand in the way of the intelligent use of atropine. The first of these is based on the typical experiment of the pharmacologist, who stimulates the vagus and perhaps the chorda tympani, and then gives a large dose of atropine, the heart rate increases and then stimulation of the vagus fails to produce its previous decrease in cardiac rate and that of the chorda no longer produces secretion of saliva. This is a legitimate pharmacological experiment, but not a therapeutic one, as the dose employed is many times larger than that used therapeutically, sufficient, in fact, to produce intoxication in man. But the student, and indeed the older text-book, retain the impression that a therapeutic dose will increase the cardiac rate. This misconception is unfortunate. A therapeutic dose, 1/150-1/75 gr (2/5-4/5 mgm), given per os or hypodermically will, as a rule, cause reduction of the pulse rate by a few beats at the end of half an hour, while a 1/50 gr may increase it by a few beats, 1/30 gr will increase it by some 20-30, and it will take 1/10 gr to have as great an effect as in the pharmacologist's experiment. With a therapeutic dose the mouth is dry but some reflex saliva can still be obtained.

The second misconception is that after therapeutic or even massive doses of atropine the vagus innervation of the gut is abolished. This has been abundantly disproved by Cushny (1), Bayliss and Stirling (2) and Henderson (3). Even small doses (0.2 mgm to a dog) decrease gut tonus but vagus stimulation will cause an increase in contractility even after huge doses (30 mgm to a dog). Similar results have been obtained for the cardiac sphincter and the colon (Langley and Anderson (4)).

The third misconception often repeated in text-books is that atropine stimulates the gut. This is due to the work of Magnus (5), who first employed the isolated gut in the water bath and found that in his experiments a concentration of 1/4000 was required to produce any effect and then an increase of movement was shown. Any modern experimenter who knows his technique, can see that Magnus, working before our knowledge of the importance of controlled hydrogen-ion concentration, had a bad bath fluid. Unger (6) in the next year produced a decrease in tonus and con-

tractility with a concentration of 1/1,000,000 or less. But Cushny, who had not used the technique, preferred to believe the famous Magnus rather than the unknown Unger and recorded Magnus' results in his text-book, yet Unger has been abundantly confirmed by subsequent workers.

The fourth misconception arises from the fact that it is assumed that Tincture of Belladonna owes its activity to atropine and that the chemical assay of the pharmacopoeias indicates atropine content. In the British Pharmacopoeia a full dose of 30 mins of Tincture of Belladonna contains alkaloids assayed as Hyoscyamine equal to 1/100 of a grain. It has been shown by Jendassik and Will (7), van Liewen and Maal (8) and others that the pharmacological activity of preparations of Belladonna are greater than the alkaloidal content if this is considered to be atropine, and somewhat greater even if considered as 1-hyoscyamine. Indeed, based on tests in our laboratory some 6-10 mins Tincture of Belladonna seem to give an effect equal to that of 1/100 gr Atropine in man. This is due probably to two factors. The chief alkaloid in Belladonna is laevo-hyoscyamine which is known to be at least twice as active as atropine, which is the racemic form, in addition, it seems probable that the other alkaloids present also increase the pharmacological activity.

The great step in knowledge initiated by Loewi (9) and Dale (10) and for which they got the Noble Prize, was that on stimulating any parasympathetic nerve fibre, acetylcholine was produced at or about its terminations. The acetylcholine then acted on the gland or muscle cells and led in turn to its activity. Further, it was shown that the sympathetic nerves to sweat glands led also to a production of acetylcholine and this is true of certain sympathetic fibres to vessels in muscles, in certain animals at least. Hence Dale suggested the term 'cholinergic' for those fibres, parasympathetic or sympathetic, which, on stimulation, liberated acetylcholine, and the old observation that pilocarpine led to the activity of sweat glands as well as all parasympathetically innervated glands or muscles, appeared in a new light. Pilocarpine activates all cholinergically innervated structures and atropine usually depresses them. The word 'usually' is used advisedly. A motor nerve to a skeletal muscle when stimulated, also liberates acetylcholine and the effect of stimulation cannot be

*From the department of Pharmacology University of Toronto
†Professor of Pharmacology and Toxicology Faculty of Medicine The University of Toronto

abolished by atropine. This is true also of the pre-ganglionic fibres, whether sympathetic or parasympathetic, which also liberate acetylcholine in the ganglion and which are uninhibited by atropine.

The dilatation of the vessels of the salivary glands on chorda stimulation persists after atropine. This might be explained on the basis that the stimulation produced acetylcholine as we know it does, and that the acetylcholine diffused to the vessels and dilated them. Dale seeks to explain the failure of atropine (again even in massive doses) to prevent the stimulation of the pelvic nerve causing contraction of the bladder by the failure of atropine to block the action of acetylcholine as it does elsewhere, and again this failure must apply to the gut, as was pointed out above. The acetylcholine hypothesis of nerve transmission is quite properly generally accepted, though there are some dissidents, but it is not to be followed too slavishly as yet.

Undoubtedly there is one thing which this work has taught us, namely, that injected acetylcholine will act on cells, gland or smooth muscle and put them into activity. Pilocarpine acts also on cells and atropine, acting upon certain cells, prevents acetylcholine from activating them.

SALIVARY GLANDS

Ivy (11) has well summed up the evidence leading to the conclusion that the salivary glands are entirely under nervous control. After atropine the effect of vagus stimulation is lost before that of chorda, although this, too, is greatly reduced, but Henderson (12) found great variability in the amount of atropine actually required by different dogs. In one case 0.1 mgm atropine sulphate intravenously to a 10 kgm dog decreased the effect of chorda stimulation from 15 to 10 drops of saliva, 0.2 mgm decreased the effect of vagus stimulation, 0.5 abolished it, but chorda stimulation was not inhibited completely. There is abundant evidence that about 1.2 mgm atropine to a man did not entirely release the heart from vagus control and that to do so 1/30 gr or 2 mgm is required. In man about 0.5 mgm usually produces a dry mouth but some reflex saliva can still be obtained. As far as can be judged, man is somewhat more sensitive than the dog per body weight, the required dose being about 0.3 mgm 10 kg for man and 0.5 mgm for the dog.

GASTRIC GLANDS

When we turn to the gastric glands and the effect of atropine upon them, the same variability in sensitivity should be remembered and secondly, it should be realized that even an intravenous dose of atropine does not exert its full effect for some minutes, while the effect of a subcutaneous dose does not reach its maximum for some 30 minutes. Orally the latent period is nearly as long. These points have been overlooked by some workers.

The gastric glands are put into activity by the so-called psychic secretion which in as far as it arises from sense endings in the mouth or nose, might more properly be called a reflex secretion. The efferent

pathway is the vagus. Secondly there are other sources, mechanical distension, secretagogue substances which act reflexly or directly on the glands. Histamine may be one of these, and finally there is evidence of a hormone, usually termed gastrin (after Edkins), which has been most persistently sought for by Ivy. A good summary of the evidence may be obtained in his papers (13-22).

Direct evidence of gastric secretion produced by stimulation has been but rarely sought. Pavlov and Schumova (14) and Uschakow (15) however, have shown that direct stimulation of the vagus leads after a long latent period to a secretion of gastric juice with high peptic activity, but low acidity, probably owing to the amount of mucus with which it is secreted. The administration of atropine abolished the effect of such stimulation. Further, it must be remembered that splanchnic stimulation also seems to produce secretion.

Hartzell (16) showed that cutting the vagi decreased gastric acidity for 5 months, but not after a longer period on the same animals (Van Zant (17)).

In animals there is evidence that atropine decreases the secretion after food has been given (Riegel (18), Keeton, Luckhardt and Koch (19)) and on the whole the acid secretion seems to be more depressed than the total amount. Lim, Ivy and McCarthy (20) found that the secretion obtained by distension was reduced by 1 mgm atropine. The secretion produced by secretagogue substances, partly purified and given in various ways, was again abolished. Gray (21), who produced a constant secretion by repeated small injections of histamine in dogs, showed that 0.5 mgm atropine subcutaneously decreased the acidity by 25%, 1 mgm by 37% and 2 mgm by 43%, but that if the histamine dosage were larger, such doses of atropine had much less effect, thus confirming Keeton, Luckhardt and Koch, and Ivy (22) who states that 1 mgm of atropine to a dog will antagonize threshold doses of histamine, but not larger ones.

Again Keeton, Luckhardt and Koch found that while 0.025 mgm atropine reduced the secretion produced by a purified but still impure gastrin, 12 times this dose did not abolish it. Klein (23) found that when secretion from a completely denervated pouch was produced by hydrochloric acid, 1-1.5 mgm per kg dog abolished it, but not if the flow was larger. Ivy and Jarvis (24) showed that protein hydrolysates administered by stomach tube caused secretion in a denervated pouch and that 1 mgm of atropine prevented it.

This brief summary of the striking evidence obtained from dogs where conditions can be closely controlled makes it evident that experiments on man are not likely to furnish more than uncertain evidence particularly when there is good evidence that psychic inhibition occurs readily, even in dogs.

The evidence of Adlor (25), Lockwood and Chamberlain (26), Rall (27) and Winkelstein (28), all using

test meals, may be summed up by saying that 0.5 mgm (1/120 gr) produces but slight reduction in gastric acidity, whether given per os or subcutaneously, 1 mgm (1/65 gr) produces more effect, and 1.2 mgm (1/50 gr) still more effect, but the individual variation is great.

Kecser and Bloomfield (29), using an alcohol test meal (50 cc 7%) found that after atropine (2 mgm) there was often a prompt initial secretion in the first 10 minutes and then a decrease from the normal. In other cases this decrease occurred earlier. The acidity also decreased.

Pollard (30) using 0.2 mgm/10 kgm, i.e. about 1.2 mgm and a histamine stimulus, found a decrease in juice volume and pepsin content.

Ciohn (31) found that 1/65 gr might increase the acidity but in 2 cases where there was a continuous secretion, the dose stopped it.

It should be remembered also that changes in acidity, as a criterion of the amount of secretion, are full of possible fallacies.

A careful study on a gastric fistula case, using various stimuli, reflex, alcohol, histamine and hydrochloric acid, with measures of total secretion, acidity and ferments (and the effect of atropine), would be of value.

It does not seem improper to sum up the impressions derived from the literature by saying that 0.5 mgm will decrease the psychic secretion more than that due to histamine or the hormone, but that the total effects will not be great, while a dose of 1.2 mgm atropine will abolish a continuous secretion, but not that found in some cases of duodenal ulcer. The same dose will decrease, to some extent, the effect of histamine and alcohol and may have some effect if a meal is the stimulus (see also Ivy 13-22).

THE PANCREATIC SECRETION

Pancreatic secretion can be produced by vagus stimulation in dogs, but as is evident in the experiments of Modrakowski (32), the amounts are small. On the whole, he obtained more response by rhythmic mechanical stimulation of the sympathetic. The small amount of secretion may be explained by the work of Korovitsky (33), who showed that in the cat the vagus contained fibres which constricted the pancreatic ducts. Popielsky (34) claimed that pancreatic secretion was as prompt on stimulating the vagus in dogs as saliva on stimulating the chorda, however he speaks of choosing certain vagal fibres or fibres accompanying the vessels in the gland, but these might be sympathetic. Popielsky states that his results could be obtained even if the pylorus were tied. There is every evidence that the secretion may, in part, be psychic.

Some of the difficulties in interpretation of the earlier workers were resolved when Bayliss and Starling (35) suggested and produced evidence for the existence of a hormone, secretin, formed by the action of acid or other substances on the gut wall and carried by the blood stream to the pancreas. Any doubt about

the existence of this hormone was cleared away by the work of Farrell and Ivy (36). Even prior to the work of Bayliss and Starling it was evident that in the dog the gastric secretion produced by taking food was reduced by atropine, for example Babkin and Sawitsch (37), Bylina (38) and Babkin (39). It is, however, clear that the effect of atropine on hormonal secretion is much less. Farrell and Ivy, for example, found that the secretion produced by giving hydrochloric acid was not reduced by 1.5 mgm to a dog, and Bayliss and Starling could not reduce the secretion from the injection of their impure secretin by atropine, and as was found by Pawlow (40) and Gottlieb (41), the continuous pancreatic secretion in rabbits doubtless due to secretin, is not reduced.

If, then, we turn to observations in man, Holsti (42) showed clearly that the prompt secretion (in one minute) on taking food and the decrease in secretion on injection of 1 mgm of atropine one hour after taking food, reached its maximum in about 20 minutes and lasted about one hour.

Comfort, Osterberg and Priestley (43) found that 1/75 gr (0.8 mgm) taken at the beginning of a meal and repeated at the end of the first and second hours, caused a decrease in secretion, especially in that of the second and sixth hours. This may, in part, have been due to an effect on gastric movements. McCaughan, Sinner and Sullivan (44) found that 1/100 gr (0.6 mgm) caused a slight decrease in a continuous secretion, as did Snyder and Liem (45) after food.

The doses employed therapeutically in man are small and it is hardly to be expected that much effect would be produced, especially when the secretion is hormonal.

GASTRIC MOVEMENT

A careful study of the literature, well summarized by Barclay (46) and Alvarez (47) and illustrated by unpublished experiments in gastric movements and by several studies of intestinal movements from this laboratory (48, 49), leads to the following condensed pictures of the movements of the stomach. Perhaps the most important change is in that of the tonus, which produces variable but not marked changes in internal pressure and to changes in form and position owing to the peculiar distribution of the longitudinal and particularly of the oblique fibres. Secondly, there are the so-called peristaltic waves, which like those of the intestine as Cannon (50) has shown, are produced by stretching, but which according to the evidence of Thomas and Kuntz (51) do not require the participation of the plexus as do those of the intestine. These waves frequently begin in the area of the incisura, but may occur in the cardia. Usually not deep at first, as they progress towards the pylorus, they become deeper and may in extreme cases cut the content in two. When a wave has progressed to within 2-3 centimeters of the pylorus, there is often a sudden contraction of this area (called a systole). Superimposed on these waves are smaller more frequent waves (wavelets of Alvarez and Zimmerman (52)). These are possibly not progressive and more or less resemble the

rhythmic waves of the intestine Just before a peristaltic wave, they are more marked and may be superimposed on it Apparently there are also waves of a slower character than either of these, the waves of tonus change The musculature of the pylorus is continuous with that of the pyloric antrum, but somewhat thicker Functionally it seems to act as a continuation of the stomach but the tonus of this region is highly variable In some cases it is almost ptulous and content passes easily, very slight peristaltic waves being enough to forward the content, but on the other hand the tonus may be high and even deep waves force little or nothing, as though the contraction of the pyloric sphincter had occurred so promptly that it prevented the passage of content The careful work of Quigley and Read (53) indicates that most of the ejected stomach content passes before the sphincter contracts, but that some passes in the early phase of sphincter contraction

The stomach is supplied with both vagus and sympathetic nerves The *vagus* there is clear evidence that vagus impulses reflexly produced by the act of swallowing cause a relaxation of the cardiac sphincter and of the cardia The work of May (54) and Cannon and Lieb (55) shows this clearly in animals and also that vagus stimulation may produce the same effect, often followed by a rise in tonus of the sphincter It is not known how far these inhibitory fibres spread over the cardia On the other hand, there is abundant evidence that stimulation of the vagi may produce increase of tonus and of peristaltic waves (McSwiney and Wadge (56), McClea and McSwiney (57)) Hence it is not astonishing that varying results have been obtained by all students of the question, but the evidence may be summed up by saying that if the tonus is high and/or movements marked, vagus stimulation produces a more or less marked inhibitory effect, at all events for a short period, while if tonus is low and/or movements slight, vagus stimulation is augmentor As the action of pilocarpine varies similarly, it seems that both types of fibres are cholinergic. The effect of atropine might also be expected to be indefinite In McSwiney and Robson's (58) work with isolated gastric muscle strips from the cat, vagus stimulation which produced contraction changed to relaxation after atropine as though augmentor actions were more readily depressed by this drug

THE SYMPATHETIC

Similar results have been obtained by stimulation of the sympathetic, but when tonus is high or movements marked, inhibition is produced and when low the reverse The work of Brown and McSwiney (59) should be noted, as they found that the frequency and strength of the stimulus produced different effects In the dog, for example, in the antrum only occasionally did low frequency produce augmentation, but usually all strengths and rates caused inhibition, while in the body of the stomach 1 per second or weak stimuli might produce increased rate of movement and some increase of tonus while more frequently a stronger

stimulation produced inhibition of tonus and movement A careful study with modern methods of condenser discharges on the two nerves might be of value

EXPERIMENTS WITH ATROPINE IN MAN

Here again we find a varying result obtained, and even more than in the experimental animal it is difficult to select the best technique (see the discussion of this problem by Neidhardt (60) The balloon technique, so often used, gives information which may or may not be adequate In the pyloric region a small well-filled balloon should record both tonus changes and peristaltic waves, but the smaller waves are not seen unless they fuse In the body of the stomach, unless the balloon lies in apposition with the walls, i.e. is large tonus changes may not be recorded and if the balloon is large and not distended fully (when it will act as a source of stimulation as it has been frequently shown that distension of the stomach does) then a small peristaltic wave may not be recorded Unfortunately, most observers have not furnished adequate details of the method used Use of the X-ray, when continuously watched, has a large subjective error and when plates are taken they show only the state at their particular time

Lasch (61), using the X-ray technique, reports that in normal stomachs if gastric tonus was high or normal, tonus was decreased by atropine 1-1.5 mgm intravenously, if low there was little change Marked peristaltic waves were decreased or abolished

Titelbaum (62), using a pyloric balloon, reports that 0.5 mgm intravenously decreases the balloon pressure (tonus) and also the large waves, but not in all cases in which higher doses were required. He brings forward the following observations which seem to be important After recording for 20 minutes, 0.3 mgm atropine intravenously was given, the waves ceased then 100 cc of gruel was given, the peristaltic waves reappeared, as one might expect from the additional stretching produced These were recorded for 15 minutes and 0.5 mgm of atropine was given intravenously with no effect, nor did a repetition of this dose produce any effect However, 1 mgm. did lead to a decrease This suggests that the effect of atropine depends on the conditions present in the stomach This work might well be repeated

Veach (63), using a balloon method, used a preliminary injection of morphine (75 mgm, $\frac{1}{2}$ gr) This usually produced an increase in tonus and movements (probably on account of a central vagus action), though in cases with low tonus the morphine might produce inhibition Atropine, 0.3 mgm intravenously, decreased the movements and lowered tonus Frequency of the recorded waves was not much changed

Quigley, Johnson and Solomon (64) in normal men recording with a triple balloon method and using an insulin hypoglycemia stimulus (which is also probably vagal), injected 1 mgm atropine subcutaneously and the movements were decreased Their results parallel

those of Wilder and Schlutz (65) in the dog with insulin stimulation Quigley (66) in another paper contrasting the effects of atropine and novatropine, found that in his cases the increase of movements produced by insulin was completely inhibited by 0.65 mgm atropine subcutaneously in about 8 minutes, the effect lasting 45 ± 15 minutes. It required 1.5 mgm of novatropine to produce the same effect.

The work of Anderson and Morris (67), who were careful to estimate the sensitivity of their patients by recording the effect of atropine on cardiac rate, again showed in fasting men varying effects, 0.05-0.3 mgm intravenously might increase the hunger movements, 0.4-1.0 caused cessation. Subcutaneously 1.2 mgm would seem to be required to produce an equal effect. They found, however, that 0.1 mgm intravenously and repeated in 30 minutes, produced an effect equal to a single dose of 0.6 mgm. Neidhardt (60) and Otvos (68) report similar varying results.

It seems obvious that the results of atropine administration on the peristaltic waves and tonus will depend on the dose and an effective one may be estimated at 0.6 mgm intravenously or 1-1.2 mgm subcutaneously. The effect of such doses will, however, in part, depend on the causation of the movements, for example the fullness of the stomach, and on the existing tonus and degree of the movements. Further, it is probable that under certain conditions of tonus smaller doses will produce some effect on the movements and on gastric emptying time.

GASTRIC EMPTYING TIME

As might be expected from the foregoing, the studies of the effect of atropine on emptying time have given highly variable results, ranging from Folley and Abbott (69) in five carefully controlled cases, who conclude that 0.4-0.8 mgm before a meal produce no essential change, to such a study as Herrin's (70) of thirteen normal cases in whom atropine about 1-1.2 mgm, given subcutaneously increased the initial emptying time in 9 out of 13 cases, and the time to final emptying in all 13 cases, the tonus was always lowered, peristaltic waves were of less depth and of the same frequency. He points out, however, that if a large meal was given, the delay was less. Lasch, too, found with doses of 1-1.5 mgm intravenously, the emptying time was greater, but not in all cases, in atonic cases the delay was greater than with normal ones and greatest in hypertonic cases. Lowy and Tezner (71), giving 1 mgm subcutaneously to children, report delay in 78% of the cases and with larger doses delay in all. Van Lierie and Northup (72) found that in young and old the results of atropine were essentially the same.

When there is pyloric spasm in infants, atropine in very small doses, 0.065 mgm, preceding a feeding, may lead to a relief of the symptoms. Eumydrine may prove even better (Svensgaard (73), MacKay (74)). As so often happens with drugs, it is easier to reduce a hypertonic state than a normal one. The tonus of the pyloric sphincter is probably reduced in these

cases more than that of the rest of the stomach or its movements.

ON THE SMALL INTESTINE

The evidence from animals and what little we have of value from man is much more consistent. The small gut shows tonus changes, peristaltic waves which certainly partake of the nature of local reflexes through Auerbach's plexus and are elicited by stretching (Trendelenburg (75)). There is little spreading of the stretch stimulus in the plexus (Henderson (48)). The third movement is the rhythmic waves or pendular movements and these often show an increase in activity before a peristaltic wave. The peristaltic wave is not preceded aborally by a fall of tonus or decrease of the rhythmic waves. These various changes in activity may give rise to various patterns of activity when judged by a balloon method. Atropine even in low concentrations (Unger and many others), decreases the tonus and in the intact dog 0.01 mgm per kg definitely decreases the tonus of the small intestine, but the effect of vagus stimulation on the rhythmic movements is unaffected. Quigley, Highstone and Ivy (76) showed that atropine decreased greatly the rate of passage of a bolus through Thiery-Vella loops of the jejunum. Gruber, Green, Drayer and Crawford (77), using Thiery-Vella loops of the ileum, found that 0.5 mgm of atropine intravenously reduced the tonus but the rhythmic movements appeared to be increased in some cases, this increase may be due simply to the lower tonus and may be seen with low concentrations of atropine in the isolated gut, if tonus is high.

Kendall and Drossner (78) in five patients, using a balloon of large size containing 40 cc under a pressure of 10-12 cm of water, which in itself would be likely to cause activity, found that in the duodenum the high tonus and frequent peristaltic waves were reduced by 0.4-0.6 mgm of atropine subcutaneously. The peristalsis often appeared more pronounced but this may also be observed in the Trendelenburg gut because the internal content is greater when the tonus falls slightly. Similar effects were found in the jejunum and ileum. The effect on tonus lasted longer than that on movements. If a barium meal was also present, the rhythmic movements and the peristalsis persisted, and if the tonus were initially high the waves became larger as the tonus fell. Using a barium meal alone in the duodenum, atropine greatly decreased the rate of passage. This too, would be expected, as a fall of tonus in the gut has the effect that it must be stretched more before a peristaltic wave arises (Trendelenburg) and this wave often fades out sooner (personal).

LARGE INTESTINE

A study of the large intestinal movements has been less often undertaken. The irregular changes in the caecum and ascending colon, as seen by X-ray examination, are probably due to rhythmic haustral movements. Peristaltic movements occur infrequently and especially under the action of purgatives, or dis-

tension, or the defecation reflex, run for long distances. Tonus in the empty bowel appears to be high as a rule.

Combinations of these changes occur and give rise to various patterns well described by Templeton and Lawson (79) and by Adler and Ivy (80) in dogs and by Adler Atkinson and Ivy (81) in man.

As shown by Adler and Ivy, 0.028 and 0.052 mgm per kg subcutaneously in dogs produces a decrease in tonus and in movements, the distal colon being more affected than the proximal. The increased tonus produced by small doses of morphine could be reduced by atropine, but that produced by larger doses was resistant.

The activity of the large gut in man was decreased by 1 mgm of atropine in the experiments of Ganter and Statmüller (82) and Katsch (83).

Jackman and Barga (84), using a balloon and water manometer technique in man, have shown that

0.6 mgm of atropine caused a fall of tonus and decrease of movements in the colon and Lium (85) has shown the same for the rectum.

Atkinson, Adler and Ivy (86) using a two-balloon method in a series of experiments on colostomized dogs and patients, found that for at least half of the time there is motor activity in the colon, of this, approximately 10% is propulsive. In the patients, 0.8 mgm atropine depressed the spontaneous motility and larger doses decreased both propulsive and non-propulsive motility. Atropine was found to antagonize the hypertonicity produced by morphine, 0.7 mgm atropine was given with 8 mgm morphine sulphate and propulsive motility was abolished for 2 hours. Non-propulsive action and tonus were decreased.

Very little of the work outlined in this review is clear cut, there is real need for the clarification of the whole picture of the movements of the gut and their response to drugs.

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Newer Concepts in the Treatment of Diabetes Mellitus with Protamine Insulin

By

EDWARD TOLSTOI, M D
NEW YORK NEW YORK

OUR experience with protamine insulin in the treatment of diabetes has led us to the adoption of certain concepts which deviated strikingly from the long established fundamentals of diabetic therapy. These were that the urine be free from sugar and that the blood sugar approach the normal level. When we attempted to treat our diabetic patients with protamine insulin, using such criteria for satisfactory control, we encountered difficulties which on further experimental and clinical study led us to other conclusions. It is the purpose of this paper to present the evidence for our newly adopted point of view.

Our guiding principles in the treatment of diabetes mellitus when using protamine insulin are

- 1 Maintenance of weight
- 2 Freedom from all symptoms of diabetes—thirst, polyuria, frequency of urination, hunger, weakness, fatigue, polyphagia, pruritus of the genitals, (chiefly in females), and visual disturbances
- 3 Absence of ketone bodies in the urine—acetone and diacetic acid
- 4 Glycosuria, we felt was desirable as its presence afforded protection from reactions

On the first three there is general agreement. The last, namely the glycosuria and its unavoidable concomitant hyperglycemia, have been extensively criticized (9).

Our observations began in 1936 when we commenced using protamine insulin in our diabetic clinic at the New York Hospital. We selected a group of our ambulatory patients and explained to them that we had a new insulin which we wished them to use. These

patients were intelligent and cooperative. Since we knew nothing of the technique for the use of protamine insulin we followed Hagedorn's recommendation, that is, the use of regular insulin in the morning, and protamine insulin at night. The logic for this technique was sound, as it is well established that the moderately severe and severe diabetics have a rising blood sugar during the night even if no food is taken (18).

A slowly acting preparation appeared ideal, therefore, as it tended to counteract this nocturnal hyperglycemia. At that stage of our therapy, we made every effort to adhere to the dicta of a sugar free urine and a normal blood sugar. Those were the established and conventional criteria. All agreed. However, when we found that with one daily dose of protamine insulin our patients revealed a glycosuria, we began to supplement the protamine insulin with regular insulin hoping in this fashion to eliminate the post prandial glucose loss. We also found ourselves juggling the diets so that our patients instead of receiving their daily dietary intake in the three equal divisions, were given an unequal distribution of the calories, as recommended by some workers in the field (17, 28). In addition we advised the withholding at breakfast of foods containing immediately available sugar, such as fruit juices (29). The results of all this maneuvering were that our patients were not free from sugar at all times, and when we attempted to obtain and maintain a urine free from sugar our patients developed most alarming and prolonged hypoglycemic reactions which were extremely subtle in onset. Thus the patients were receiving multiple injections of insulin, they were burdened with additional dietary instructions and they

*From the New York Hospital and the Department of Medicine
Cornell University Medical College
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lived in apprehension as reactions were unpredictable if the urine was kept sugar free. Up to this point protamine insulin was of little help to our patients and we were keenly disappointed as our aim was one injection daily. We felt that such a procedure would permit the patient more freedom as it would obviate multiple injections and free him from the slavery of the definite time relationship between the insulin administration and his meals.

During our periods of observation, some of the patients treated with one daily dose of protamine insulin failed to report at weekly intervals as was their routine. While away they kept a record of their urine analyses—fractional specimens whenever convenient. When they visited the clinic after a two, three or even four week absence, the reports revealed a yellow or orange test—four plus—at all times. The patients stated that they “never felt better and stronger.” They had to “force themselves to drink water,” they enjoyed their food but the hunger was not extreme, and if it were not for the “terrible” urine tests they would not have come for a checkup. They certainly enjoyed the new freedom of one injection a day. It was most impressive to have a record of a continuous heavy glycosuria and a singular freedom from any and all the recognized clinical symptoms of diabetes. The patients were not too happy about the glycosuria and reasonably so, as we ourselves had always pointed out to them that continuous excretion of sugar would lead to numerous dangerous complications. Such was the accepted hypothesis, it was postulated by men of reputation and authority, and we, as others, perpetuated these dicta as we neither had the experience, facts, nor the courage to challenge them. However, it was difficult to reconcile even the suggestion that patients could reveal a heavy glycosuria for weeks and yet be symptom free. Were not polyuria, frequency and polydipsia results of a constant glycosuria? Why didn't they develop ketosis and coma? We argued that perhaps the time of the observation was insufficient for symptoms to develop and after acquainting the patients with our plans and aims, they were willing to continue on the prescribed routine. These observations were then extended for two and three months in the Out Patient Department, and since this longer period of study supported our earlier observations that the patients were symptom free and gained weight, on one dose of protamine insulin, in the presence of a continuous heavy glycosuria we decided to continue this work under the most carefully controlled experimental conditions. For this purpose Dr. Eugene F. DuBois to whom I am most grateful for his cooperation and guidance, made two beds available in the metabolism ward of the Russell Sage Institute of Pathology at the New York Hospital. The results of these investigations were published (37, 38). Briefly, we studied two severe diabetic patients who received one dose of protamine insulin daily as well as a diet of 1640 calories composed of 75 gms. of protein, 60 gms. of fat, and 200 gms. of carbohydrate. One of the patients was given

50 units daily, the other 60. Both patients revealed practically a continuous and constant glycosuria—as high as 100 to 150 gms. in 24 hours on certain days—their blood sugars were consistently high throughout the day, yet they were amazingly free from any and all symptoms of diabetes mellitus, they maintained their weight, were in nitrogen equilibrium, and the urine was free from acetone and diacetic acid. These original data have been repeated with similar results (39). Such facts were startling and certainly unorthodox. They contradicted all established concepts, and suggested that perhaps with the use of protamine insulin a glycosuria may not be incompatible with satisfactory therapy. They further suggested that with protamine insulin there was satisfactory utilization of foodstuffs to maintain weight and nitrogen equilibrium even though sugar was excreted. Thus we reasoned that the factor of utilization was the dominant one and our entire plan of therapy was therefore designed to use a liberal diet and sufficient protamine insulin to achieve our criteria outlined above.

With this background we have extended the technique to our out-patient department where a considerable group of diabetic patients have enjoyed this method of therapy. Not only did the majority of them maintain their weight, but many gained. There were no complaints referable to their diabetes in spite of the glycosuria. They are in good health, in a state of social and economic usefulness, and infections among them are no more frequent than in the average individual. All these patients enjoy their freedom as there appeared no necessity for careful dietary measurements, and it is not necessary for them to carry their insulin and syringe with them. They administer the insulin to themselves in the morning and then put the equipment away until the following morning. These patients are not singled out as a group apart from their fellow men, and their habits of living approximated the normal.

THE ROUTINE OF THE CLINIC

When a patient is referred to us either with the diagnosis established or for diagnosis, a careful history is recorded. Then a thorough physical examination is done, Oscillometric records are made whenever indicated. A routine serological test for syphilis is done, urinalysis, and in addition to the diagnostic blood sugar determination, other blood chemical constituents or morphology as suggested either from the history or clinical findings. If on the first examination, the patient reveals clinical symptoms of diabetes as well as a glycosuria and ketonuria, we urge that he enter the hospital. If, however, he does not show acetone bodies in the urine we continue the treatment in the out-patient department. The very initial step in our experience has been the assurance of the patient, as on his first visit he is quite upset. Most usually he consults us after the diagnosis has been made and he has a number of questions as to what “he heard diabetes does to people.” His queries are explained as honestly as our knowledge permits, and we only dwell

on the features of the disorder that have been established and are not controversial. We tell him that the diabetes will not interfere with his work, and we point out that furthermore his expected life span need not necessarily be altered. We tell him that his social and civic and athletic activities can be continued. Of course, we point out that his food habits may have to be revamped and that he may need insulin. Most patients are satisfied with the simple explanations of what is diabetes when they are told that the difference between them and the non-diabetic is that the latter manufactures enough insulin for his needs, while the diabetic does not, and, therefore, requires additional insulin by injection. He is assured that insulin is not "dope"—as a good number still think that—and that it is effective only when given by hypodermic. We impress him with the fact that there is no oral diabetic remedy as yet. As for his diet, we tell him that he will feel the pinch little as we are quite liberal and that he will only have to give up many concentrated sweets. We then suggest a diet based on the established protein and caloric requirements, which are 2/3 to 1 gram of protein and 30 to 35 calories per kilogram, respectively. We use a liberal carbohydrate diet, 200 to 300 grams. The dietetic staff help the patient in the construction of the diet and instruct him in the approximate quantities and portions of the various dishes. No weighing of food is recommended to the patient as this procedure is, from our experience, unnecessary and not very practical. Some physicians recommend the use of scales in the early education of the diabetic to acquaint him with the magnitude of each serving. We have no objection to this method, but we feel that it holds no particular advantage over the use of household measures. In addition we have a group of wax models which have been useful in conveying to the patient the size of the serving advised. All such refinements are unnecessary for office practice as there are available many charts and tables from which a diet can be formulated, and with the use of protamine insulin too fine calculations are entirely wasteful, as at best most patients eat approximately and not too specifically what has been prescribed. Having arranged the trial diet for the patient we now direct our attention to the question of insulin administration, as in our clinic it is only the most occasional diabetic who manages his situation by dietetic measures only. As a rule in such patients the diabetes is extremely mild.

Let us assume that our diabetic has symptoms as well as a glycosuria. We then formulate his diet as outlined above and prescribe 15 or 20 units of protamine insulin, and at this point he is instructed how to administer insulin to himself. Furthermore, he is warned that if any unusual symptoms or sensations make themselves felt, no matter how trivial, he is to take something sweet at once and follow it up with either a glass of milk or a slice of bread. Then as an additional precaution all our patients taking protamine zinc insulin must have a bed time feeding, usually a glass of milk and three crackers. This serves as a

buffer for nocturnal reactions. After we are satisfied that the patient understands our instructions he is requested to return in a week. On his return, his weight is recorded, urine examined for sugar and acetone, and he is questioned concerning any symptoms which he may have had during his absence, with emphasis on those of diabetes mellitus or hypoglycemia. *If he is symptom free, maintaining his weight or is gaining, and has no acetone in the urine on the prescribed diet and insulin, and furthermore, is socially and economically useful, his treatment is considered satisfactory, regardless of the glycosuria.* If, however, in addition to his glycosuria he is losing weight, on an adequate diet, or in addition to the glycosuria has such symptoms as thirst, frequency, or weakness, the dosage of protamine insulin is increased by five units every three days until symptoms disappear and the weight has leveled off at his optimum weight. The latter can be determined from the history as to what his weight was before the diabetes set in. This too has to be judged nicely so that the patient's ultimate weight is not on the very heavy or light side. It has been our experience that most patients reach a certain level and maintain it within a range of about 2 or 3 Kg. Occasionally, because of a slight cold which is not incapacitating, or without any apparent cause, the patient may show a trace or one plus (1+) acetone. This patient is not hospitalized, particularly if he has been trained. He is told to take salty broths freely, furthermore, he is given salt in tablets or capsules, one gram every two or three hours. Each dose is followed by a glass of water. At each voiding he tests his urine for sugar and acetone and as long as acetone continues to be positive, he supplements the basic daily dose of protamine with regular insulin. If his test for sugar is yellow or red (4+), he injects 25 units of insulin, if green to yellow (2+ to 3+) 15 units, if blue or negative he takes the juice of an orange. This routine is employed *only* if and when acetone appears. Of course, if an infection is severe or the patient has not been trained we emphatically state that the hospital is the place of choice when ketosis supervenes. Little attention is paid to the blood sugar from a therapeutic angle and the glycosuria is disregarded. We emphasize, however, the maintenance of weight, freedom from symptoms and absence of ketosis. We also warn the patient of the seriousness of any infection or gastric upset and of the importance of never reducing or discontinuing the use of insulin unless so ordered.

There is no question that the above plan is a departure from the so called orthodox or conventional method of treatment—particularly the guiding features for "good control" because as stated at the outset in the past every effort was directed at a normal blood sugar and a urine free from sugar. Such aims were insisted upon by leaders in the field as they were of the set opinion that hyperglycemia and glycosuria were contributors to numerous complications of which infections, atherosclerosis and coma were the most

dreaded. Such teachings are still perpetuated today, even though the most ardent protagonists of these hypotheses admit that positive proof is lacking.

INFECTIONS

What about the susceptibility of the diabetic to infections? In the pre-insulin era, the clinical observation was that the diabetic was more susceptible to skin and other infections, and that such infections were stubborn and recurrent. These views were then handed down. The thought was that a hyperglycemia was conducive to bacterial growth and multiplication and since the "uncontrolled" diabetic had a high blood sugar, the assumption was that this medium offered bacteria a more fertile soil. This view was not supported by evidence. Handsman (16) found that blood glucose concentration up to 1% was neither a better medium nor was such blood less bactericidal against staphylococci than normal blood. This was confirmed by Hirsch-Kauffmann and Heiman-Trosien (19). Mosenthal (25), Bayne-Jones (4), and Richardson concur that hyperglycemic blood is not a more favorable medium for bacterial growth. Also Marble, White and Fernwald (22) stated that the present day diabetic patients are not more susceptible to infections than non-diabetic individuals. From most carefully planned and well presented experimental evidence they concluded that "whole blood of diabetic patients were found to possess essentially the same phagocytic, bacteriostatic and bactericidal power against selected strains of streptococci as blood from normal controls." From such observations one is led to the conclusion that the glucose concentration of the blood and tissues was not the sole likely cause for the greater susceptibility to infections, as we still see thousands of diabetics with abnormally high blood sugars who have no more infections than non-diabetics. The difference, however, between the present day diabetic and the one in the pre-insulin era is not the blood sugar only, but his state of nutrition. Today he is strong and well nourished, then he was weak and emaciated. Today he is active, irrespective of the severity of his diabetes, then he was inactive and a semi-invalid, often bedridden. It seems logical to postulate that this weakened emaciated status of the patient was conducive to infections. Such an hypothesis is reasonable as our well nourished patients, even though their blood sugar is abnormally high, have no more infections than the non-diabetics whose nutritive state is comparable. Recently, a more attractive hypothesis in connection with skin disturbances has been proposed by Rudy and Hoffmann (33). From careful clinical studies they concluded that the increased susceptibility of the skin to infections was not related to the hyperglycemia, but to a deficiency in the components of Vitamin B complex particularly nicotinic acid. They treated diabetic patients with skin lesions, with large doses of nicotinic acid and even though the glycosuria remained abundant, the skin improved. When, however the nicotinic acid was discontinued, the skin infections recurred. These ob-

servers also stated that though such skin involvement may improve when the glycosuria is eliminated it may remain unchanged or become worse even though the diabetes is "controlled." But the use of appropriate doses of nicotinic acid always induced healing irrespective of the diabetic status.

There has also been much discussion about the healing of wounds in diabetic patients, and surgeons have been reluctant to operate on patients whose blood sugars were elevated. It was, and still is stated categorically, that wounds in uncontrolled diabetes healed with difficulty, and because of this, diabetic patients requiring surgery were poor risks. Since it was accepted that the hyperglycemia and glycosuria were the causative factors in such instances, all efforts were directed towards rendering the patient free from sugar before an operation. Dentists were loath to extract teeth for similar reasons. All of this may have been tenable in the pre-insulin era. Today our experience is quite to the contrary. We can unequivocally state that our protamine insulin treated cases—well nourished and hydrated—exhibited no delay in the healing of their surgical wounds. Our patients were subjected to laparotomies, mastoidectomies, cholecystectomies, thoracotomies and other major procedures. The healing of the incisions or post-operative course were neither longer nor different from the normal. Many of our cases revealed a glycosuria continuously post-operatively and yet healing was satisfactory. Green, Swanson and Jacobs (14) studied the relation of the incidence of delayed healing of clean and infected wounds to the height of the blood sugar and degree of glycosuria in 324 patients with diabetes and found no relationship between the height of the blood sugar and degree of glycosuria, to the healing or infection in clean wounds. In general, however they found that "delayed healing of wounds occurs approximately 4 per cent more frequently among diabetic than among non-diabetics of the same age and sex." It is obvious that the well nourished and "healthy" diabetics treated with protamine insulin, and the well hydrated surgical diabetics even in the presence of a glycosuria and hyperglycemia, are not more susceptible to infections or surgical hazards than the non-diabetic. We do not imply that the diabetic requiring a surgical procedure should be disregarded. He should be properly prepared, if time permits. By that we suggest salt, fluids and ample carbohydrate—all by mouth, as well as insulin. This attack will insure hydration and rich glycogen deposition both of which are of tremendous safety to the diabetic. However, a glycosuria and hyperglycemia are no contraindication to emergency surgical necessities, and a glycosuria throughout the post-operative course is not conducive to delayed healing or infections, if hydration is maintained and sufficient insulin given to prevent symptoms of diabetes. The glycosuria under such conditions is not harmful.

VASCULAR SCLEROSES

Evidence that hyperglycemia and glycosuria are the etiologic factors in the vascular degenerative lesions

is not convincing. Though the older diabetic patient reveals a picture of extensive vascular degeneration, it does not necessarily follow that the hyperglycemia and glycosuria are the responsible factors. Might not the diabetes be another manifestation of a generalized vascular disease? Proof for such an assumption might be offered as justifiably. The techniques used to appraise the vascular system have been of two types, one, roentgenograms of the soft tissues of the extremities, two, ophthalmoscopic examination. Morrison and Bogan (26) found 53 per cent of 324 diabetic patients showed calcification of the vessels of the lower extremities. Enklewitz (11) analyzed these statistics critically and found that of 121 cases under the age of 40, only five were positive. Furthermore, of the 25 patients under the age of 40 who had diabetes for 5 years or longer only 3 showed calcified vessels. In the older group—the fifth to the eighth decades, calcification was most marked. Bowen and Koenig (5) studied the leg vessels of 58 diabetic patients who were not receiving insulin. In these cases the diabetes was less than 5 years' duration. Of these, 17 showed calcium deposits in the vessels of the feet, and 14 of this group were between the ages of 60 and 80. Of the 20 patients under the age of 40 years only one showed calcification. Boyd, Jackson and Allen (6) studied the roentgenograms of the soft tissues of the wrists or ankles of 69 children and found no evidence of arteriosclerosis in any subject. These subjects represented controlled diabetes in the absolute sense. Nevertheless, the authors admit that the degree of cooperation varied and that even the most cooperative had single or repeated intervals of non-control. Evidently such breaches were not at all conducive to vascular sclerosis as none were demonstrable. We have observed roentgen evidence of calcium deposits in the tibial vessels in a young diabetic patient, whose diabetes was only two months old, and we could not find this vascular change in patients with severe diabetes from 5 to 12 years' duration who revealed glycosuria most of the time. These patients were receiving insulin and were well nourished. Experimentally, the above observations were substantiated by MacLeod (21). He could not demonstrate vascular lesions in depancreatized dogs which were maintained in a good state of nutrition by means of insulin, but revealed hyperglycemia and glycosuria for over four years, and he estimated the four years of the dogs' lives corresponded to twenty years of man's.

The view that retinal changes were due to hyperglycemia is not too strongly championed today. Most ophthalmologists are of the opinion that the retinitis found in diabetes is the retinitis of arteriosclerosis. Wagner and Wilder (40) studied 44 cases of retinopathy with diabetes. Of these only two were under 40 years and they had systemic disturbances which readily accounted for the retinal change. Dixon (10) studied 68 diabetic patients because of ocular complications and found that most of them had an arteriosclerosis. Gresser (15) observed 100 cases of diabetes mellitus and stated that "the retinopathy seen in

these diabetics did not conform to one clear picture, no entity having been established. The majority showed characteristics of hypertensive retinitis, both vascular and exudative. No relationship was seen between the presence of retinopathy and the severity of diabetes." Anderson (2) discussing the problem of retinitis in the diabetic patient, expressed the view that neither the age of the patient nor the most ideal therapy with diet and insulin will "exempt the diabetic patient from eligibility." Boyd and his associates (6) reported on one patient of 69 studied in whom ophthalmoscopic examination revealed evidence of arterial disease. This was a 20 year-old female who had diabetes for 18 years. However, she presented so many abnormalities including hypertension, albuminuric retinitis, and uremia, that the retinopathy might have been but a single unit of a generalized vascular process.

KETOSIS AND COMA

The blood sugar in diabetic ketosis and coma is elevated. Usually, there is a marked glycosuria as well. Such findings have led to the hypothesis, that a hyperglycemia and glycosuria are contributory factors in the development of keto-acidosis and coma. This hypothesis was popular during the pre-insulin era, but more recent studies have shown that it is not tenable. Excellent publications dealing with the subject of ketogenesis have been presented by Baines and Drury (3), Chaikoff and Soskin (8), Friedmann (12), Mackay (20), Mirsky (23), Stadie (36), and others. Our interest in ketogenesis is concerned chiefly with the part that hyperglycemia plays in its mechanism. Is there experimental or clinical evidence that the hyperglycemia contributes to ketone production? A presentation of the available evidence is in order.

It has been shown that glucose given intravenously to depancreatized dogs caused a fall in the ketone bodies of the blood and urine. Conversely, when glucose infusions were discontinued the ketonemia and ketonuria increased. Similar observations have been recorded in patients treated with and without insulin, to whom large quantities of carbohydrate were fed, and as a result hyperglycemia and glycosuria noted (24). We have reported such observations (39) quite independently of others. From our experience and the experimental results of others we are of the opinion that with the proper use of protamine insulin, hyperglycemia and glycosuria are not at all deserving of the attention previously given them. We have seen no deleterious effects among our patients whom we have observed for over five years. On the contrary, a great number gained weight and enjoyed more freedom because their living habits approached more closely those of normal individuals.

It may be argued, and justly, that since we direct our efforts towards making the lives of our patients normal as to living habits, why not extend our efforts in the direction of physiologic normality so far as the diabetes is concerned, that is towards obtaining a

urine free from sugar and possibly a normal blood sugar, throughout the day. Can that actually be accomplished in the moderately severe and severe diabetic individual who is ambulatory and not under constant supervision? Our experience has been that not only is it almost impossible, but it is not at all necessary because of the availability of protamine insulin. To quote Richards (30) as to the practicability, who writes "But whether or not it is so desirable to keep diabetics free from glycosuria and hyperglycemia, as a matter of fact, in spite of all our efforts the average patient does not do so. While we have him in the hospital we go to a good deal of trouble to achieve this ideal and try to impress upon him its necessity, but after he goes home, feeling well, he generally gets impatient with all the fuss and lapses into dietetic sins. He quits weighing or measuring his food, trusting to his memory of what proper amounts look like and only tests his urine on rare occasions. Usually he tries another doctor or two and even, if his financial condition permits, journeys to distant places of repute, getting different food prescriptions at each, at one a low carbohydrate-high fat, at another, high carbohydrate-low fat, and various compromises between the two. Ultimately he settles down, largely to his own devices, varying his diet as he feels inclined but mostly continuing his insulin in amounts determined by his feelings, and in spite of it all, in the majority of cases he gets along very well, though most of the time he passes sugar. At times he gets into trouble and returns for advice or help, but, the emergency over, back he goes to his own methods. In fact, it has been a matter of surprise to me, impressed with the need of keeping him sugar free, how well he really does." Is it imperative from physiological consideration to aim at a normoglycemia and a urine free from sugar when using protamine insulin in the treatment of diabetes? Our experimental and clinical evidence (37, 38) proved that was not the case. We were not concerned with how much glucose was excreted but how much *was retained*. After all what we are after is aiding the diabetic in the utilization—oxidation and storage—of a quantity of foodstuffs compatible with his individual metabolic needs. If this is accomplished our efforts are in the right direction.

Peters and Van Slyke (27), define diabetes mellitus as a condition in which the maximum attainable rate of carbohydrate combustion is reduced below normal and the ability to store glycogen after glucose or starch were fed, is lost. There was nothing in this definition about glycosuria or hyperglycemia. *The emphasis was on utilization.* Since the basic defect according to this excellent definition is a diminution of carbohydrate combustion and storage, any measure or agent which corrects this defect, tends to remedy the disturbance. Insulin does just that. Regular insulin restored the normal physiology for the duration of its pharmacologic activity which at best was 4 to 6 hours. The diabetic was assured, therefore, of improved

carbohydrate metabolism for this short period even though he excreted sugar. Today one can prolong the utilization—that is the combustion and storage of carbohydrate—by means of protamine insulin for a 24 hour period. If, then, the metabolic processes have been so altered that the diabetic can attain a carbohydrate metabolism approaching normality, everything else is of minor consideration. True, he may and does reveal a glycosuria and hyperglycemia, but the more important feature is that with the aid of protamine insulin he is utilizing carbohydrate better than ever before and over a longer period of time. The crux of the matter is not the excretion of glucose, but rather its *utilization*. This most important factor of utilization has been ignored although it was first emphasized by DuBois (1) and his associates in 1914. They presented calorimetric studies on a severe diabetic patient, showing that on a high carbohydrate diet, (250 gms—that was in 1914), he could and did utilize this food stuff in the presence of a hyperglycemia and glycosuria. Such utilization was quantitatively below the normal level, but the undisputable and unalterable fact remains that even without insulin there was sharply defined evidence of carbohydrate utilization in the presence of a hyperglycemia and glycosuria. This fact has been corroborated by many. Bridge and Winter (7) also studied this factor of utilization and demonstrated that there was no correlation whatever, between the height of the blood sugar and the respiratory quotient in cases of diabetes treated with insulin, and they emphasized that carbohydrate was not utilized at different rates whether the blood sugar was high or low. A high blood sugar did not impair the utilization of carbohydrate. From such observations they too, and independently of us, concluded that neither the value of the blood sugar nor the degree of glycosuria is an adequate criterion for the regulation of diabetes.

We see as shown above, diabetic patients who receive one dose of protamine insulin daily, and who in spite of a continuous hyperglycemia and glycosuria do well and are free from ketosis. The reason is an interesting point for speculation. It is our thought that, provided each patient metabolizes—oxidizes and stores—a quantity of carbohydrate essential for his particular needs, his metabolic processes will approach the normal state. It is most important that such an optimum of carbohydrate, no matter how small, be utilized, otherwise symptoms of diabetes and ketosis will supervene. By giving enough protamine insulin to insure the utilization of this necessary quantity restoration and maintenance of a metabolic state *approaching normal* is achieved.

SUMMARY

We have presented our criteria for the satisfactory treatment of diabetes mellitus when using protamine insulin, and have described the details of the method used in the outpatient department at the hospital. The

basic principle was the quantity of glucose utilized and not excreted, and the evidence for such utilization were maintenance of optimal weight, absence of diabetic symptoms and absence of urinary ketones. Furthermore, we have discussed the complications attributable to hyperglycemia and glycosuria and have shown that the evidence for such assumptions is inferential and inconclusive. Therefore, we have not insisted on a normal blood sugar and a sugar free urine, as our experience over a five year period has led us to the con-

clusion that such rigid demands are not necessary. Our patients treated with protamine insulin in spite of the constant glycosuria were socially and economically useful. They developed no more frequent nor more severe infections, and when surgical measures were required, their wounds healed as readily as normals. When, however, we tried to adjust the glycosuria too finely or maintain the urine free from sugar, unpredictable and disconcerting reactions occurred.

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Pruritus Ani

By

ALFRED J CANTOR, M D

FLUSHING NEW YORK

THE syndrome of pruritus ani has suffered from the same difficulties that long confused the syndrome of epilepsy. Pruritus ani is no more a disease than is epilepsy. Both are symptoms. In the former itching is the chief manifestation, while in the latter the outstanding manifestation is the convulsion. Just as certain cases of epilepsy are due to brain tumor, syphilis, cerebral trauma, etc. so certain cases of pruritus ani are due to ova infestation, allergy, eczema, chemical irritation, rectal pathology, etc. Further, just as in certain cases of epilepsy the basic pathology cannot be determined, so in certain instances of pruritus ani the etiology cannot be determined by present diagnostic methods.

For those cases without evident etiology I would suggest the term "cryptogenic pruritus ani." This is more suitable than idiopathic pruritus ani, for the latter would indicate a disease without a cause, a type of spontaneous generation. Cryptogenic pruritus ani, in contrast, signifies simply a disease of unknown (i.e. undetermined) etiology. In this group would be classified all cases of undetermined etiology only after exhaustive general and local examinations.

All other cases would be classified as "secondary pruritus ani," and thus there would be only two all-inclusive groups, cryptogenic and secondary. The importance of such a classification is quite obvious. First, it makes evident the fact that there are certain cases of pruritus ani which, despite exhaustive study, must ultimately be placed in the category of undiagnosed etiology. These cases of cryptogenic pruritus ani represent failures of our diagnostic armamentarium. Treatment, of necessity, must be empirical in all such cases. Such a classification renders exhaustive study and complete examination, both local and general, an absolute necessity before cataloguing of each individual case. Further, this classification would tend to obviate much of the confusion in the literature on the diagnosis, etiology and therapy of various forms of pruritus ani. Thus, both directly and indirectly, it provides a practical guide not only for diagnosis but also for therapy.

ETIOLOGY

A review of recent literature reveals a variety of concepts with regard to the etiology of pruritus ani. In terms of our classification all subsequent discussion, unless otherwise stated, will refer only to secondary pruritus ani.

Allergy is commonly (1, 21, 6, 10, 19, 18, 26, 3) a prominent consideration in etiology. It is accepted that allergic hypersensitivity is basically hereditary.

Of course susceptibility to a particular allergen may be either inherited or acquired. The most common food allergens include egg, milk and milk products, wheat and wheat products and chocolate. Ingestion of a large quantity is unnecessary, for a mere trace of the offending food may produce severe symptoms. Drugs may bring on attacks, and occasionally non-proteins such as alcohol. It is noted that itching and increased irritability are characteristic of all allergic conditions (21). Some authors (6) conclude that the vast majority of cases of essential pruritus (cryptogenic pruritus) of the anus and vulvae are due to eczema. Eczema is a manifestation of skin hypersensitivity, i.e. the patient's heredity. The activating cause however, may be chemical, (drugs, dyes), clothing, hemorrhoids, diet, heat, perspiration and friction and atmospheric conditions. Thus, these authors would seem to state that the vast majority of pruritus ani in which the etiology cannot be determined (cryptogenic) are actually on an allergic basis with one of a variety of precipitating external causes. In such a concept these cases should actually be classified as secondary pruritus ani.

Inhalants must also be mentioned as potential allergens. They are probably not of great importance in the consideration of allergic pruritus ani.

Positive patch-test reactions to solutions of indol, scatol and fecal emulsions from patients with active pruritus ani are considered to be evidence of a specific sensitivity in these cases (18). Constant fecal soiling may thus account for recurrence of symptoms after symptomatic relief by sensory nerve block.

It should be noted that the histopathologic picture in pruritus ani is comparable to that of allergic skin manifestations (19). The acute onset is characterized by cellular infiltration beneath the rete malpighii, spongiosis among the prickle cells, parakeratosis and beginning lichenification of the stratum corneum. The chronic picture reveals acanthosis, the papillary bodies are narrowed and later show fibrous change. Spongiosis decreases and lichenification increases. Hair and sebaceous follicles are plugged. Sweat pores of both eccrine and apocrine glands remain patent.

Buie (3) believes that the most likely cause for skin changes in pruritus ani is the direct effect of bacteria and their toxins or both. Often there is a direct connection with trichophytic disease elsewhere. An important factor in many cases is fungus infection (5, 10). Indeed, it is suggested that inasmuch as 20% of all cases of pruritus ani are associated with mycotic infections one-half strength Whitfield's ointment should be employed as routine treatment (18). Win-

field demonstrated the streptococcus fecalis and colon bacilli in 90% of anogenital pruritus (26)

Oxyuris infestation is a common cause of pruritus, particularly in children (13, 12, 10, 4) Indeed, the threadworm is said to be the most common cause in children (13, 4) One or more of these worms may be seen at the anus or through the proctoscope They tend to come from higher up in the rectum or anus toward evening Oxyuriasis is produced by Oxyuris vermicularis development in the intestine The female worms wander out of the anus to cause pruritus The eggs are carried on the fingers to the mouth, producing autoinfection Eggs may be ingested with contaminated food or from soiled clothing The anal mucus membrane may be congested, studded with small worm bites, and is often covered with blood-stained mucus The rectal mucosa may show a catarrhal inflammation Diagnosis is by finding worms or the eggs in material

anal canal disease Mucus, pus, blood or mineral oil seepage may produce local mechanical and perhaps chemical irritation Rectal constipation with imperfectly emptied rectum, even after apparently normal evacuation, may allow the passage of frequent flatus with mucus A fecal mass resting on the pile-bearing area may produce hyperemia and thus produce a slight excess of mucus (4) One author (18) found rectal constipation with fecal soiling to be so frequent that a rectal enema after defecation and at bedtime is advocated as routine treatment Another states (14) that rectal constipation is the most common cause of pruritus ani In a series of 131 cases (109 males and 22 females) digital examination revealed an ampulla filled with feces in 114 cases, in spite of no history of constipation

Local irritation by clothing is another factor for consideration Anal skin tags increase the likelihood

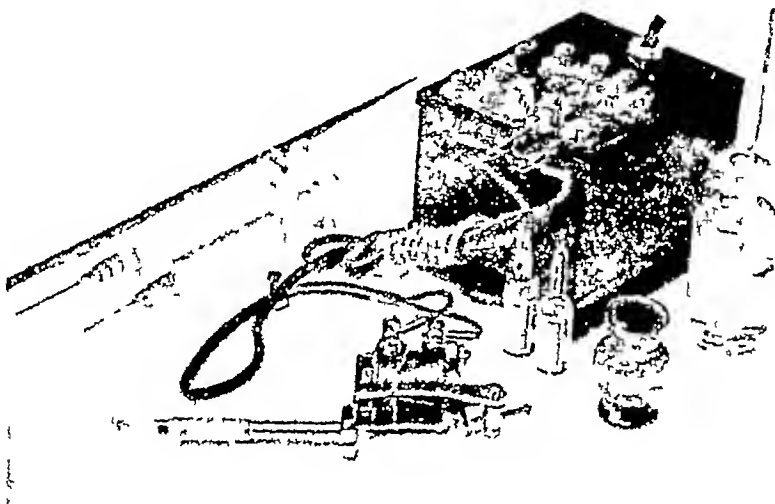


Fig 1 Instrument Tray for Tattoo Tattoo apparatus, transformer, oil-soluble anesthetic ampoules, mercuric sulphide jar, alcohol, and syringes for aqueous and oil anesthetics

scraped from the verge or perianal area The "N I H" swab is useful in diagnosis This swab consists of a glass rod with a one inch square of cellophane folded over one end and held by a rubber band The cellophane is used to scrape the perianal skin A drop of tenth-normal sodium hydroxide is placed on a glass slide, the cellophane is placed on the drop and released by removing the band with forceps, and is then flattened on the slide and covered with a cover slip for examination

Pediculus pubis is said to be the most common parasite in the experience of one author (4) He further states that a fungus or yeast is a very rare cause Scabies is also offered for consideration as a possible etiological factor

Mechanical factors are of great importance in every case Excessive moisture may irritate the skin due to lack of cleanliness, excessive sweating, or may originate from within the bowel as a result of rectal or

of lack of cleanliness and probably favor excess sweating Dyes in clothing, irritating soaps or starches used in washing of under-garments or baby diapers, the wool content of clothing, or synthetic fabric sensitivity must all be included in the consideration of local mechanical or chemical irritants

The action of local secretions, as sweat, an over-alkaline or over-acid urine, is probably both mechanical and chemical In the same category must be included diabetic urine, urine containing calcium or oxalate crystals, and vaginal or fecal discharges Any of these mechanical or chemical factors although apparently minor, as excessive sweating, may be followed by scratching and ultimate severe dermatitis, thus inaugurating a vicious cycle Such cases, when observed in their late stages, would present no obvious etiological factor They would probably be classified as cryptogenic at that time Caution must be exercised in the interpretation of bacteriological studies in such

cases. Organisms revealed at this stage would be secondary invaders, and although they might further the vicious irritative cycle they would not be of primary causal importance.

The influence of general metabolic changes in the production of general pruritus and pruritus ani is worthy of consideration. The allergic factor has already been discussed. Rare cases are reported with an achlorhydria, diminished Vitamin A absorption (Swift), with deficient nutrition of epithelium (4). Lack of Vitamin B absorption may produce altered nerve ending sensation.

Retention in the skin of abnormal products of metabolism, as nitrogen retention in kidney disease, may be a factor (10). Functional kidney disturbances with nitrogen retention are to be considered apparently in women more than in men (26). Pruritus may occur in insufficient hepatic function with or without icterus, apparently due to saturation of the blood with bile.

In diabetes there is a direct relation between pruritus and hyperglycemia (26). In a uric acid diathesis hyperacidification of the blood, according to Pulay, produces imbibition of the tissues with a sensory and sympathetic vascular irritant. In 200 cases of pruritus or eczema Schumberg and Brown found an increase of blood uric acid in 44%.

Endocrine dysfunction may cause substances to enter the circulation and thus increase sensibility of sensory nerves, leading to itching in the presence of local irritation. Thus diabetes, exophthalmic goiter and the menopause must be considered.

The taking of excessive food, either directly or by the development of intestinal toxins, is said to be a potential factor (1). Deficient functional activity of digestive secretions may produce imperfect oxidation of important food elements. Any digestive upset may thus precipitate an attack. Rich diets and alcohol (4) are other general factors.

A local biochemical approach to the problem is offered by the observation that epidural injection of 20% magnesium sulphate cures most cases of pruritus ani (16). It is observed that such an injection adds magnesium ions to the biochemical structure of the cauda equina, thus restoring a disturbance of the calcium and magnesium ion equilibrium. In two cases so relieved pruritus returned after intravenous injection of calcium gluconate. Thus it is believed that pruritus ani is a syndrome linked with various causes capable of acting on the sympathetic nerve in general, or on the sacral sympathetic by local causes. It is noted that epidural injection of novocaine, although interrupting the nervous paths much more effectively than magnesium sulphate, has no effect on the pruritus.

There remains for consideration the psychogenic form of pruritus ani. This type of pruritus ani may be a manifestation of hysteria, anal masturbation or other psychosis. The treatment of this group of cases

is extremely difficult. They are usually complicated by other factors, particularly trauma (self-inflicted) and secondary bacterial infection. In such cases even after the local condition is completely cleared, and sometimes even after a neurotomy or tattoo the sensation of pruritus persists. Hopkins (22) reported six cases of skin diseases with pruritus in which the cause was largely, if not entirely psychogenic. Sack (20) states that pruritus may appear as a genuine hallucination, and is a very common symptom in endogenous and relative depression. This hallucination may be provoked easily, suggestively and auto-suggestively. Senile pruritus is often an expression of a state of senile depression. Sexual neurosis must also be considered. These cases illustrate the necessity of combining the dermatologic, the protologic and the psychiatric approach in the treatment of certain cases of pruritus ani.

CLASSIFICATION

The following classifications are offered in review of the factors discussed.

General Etiological Classification

- I Cryptogenic
- II Secondary
 - 1—chemical
 - 2—mechanical
 - 3—bacterial
 - 4—psychogenic
 - 5—allergic
 - 6—physical
 - 7—metabolic

Specific Etiological Classification

- A Cryptogenic Pruritus Ani—usually associated in vicious cycle with relief trauma (i.e. scratching)
- B Local Rectal Factors

1—rectal constipation	} mechanical (traumatic)
2—fissure	
3—fistula	
4—cryptitis and papillitis	} chemical
5—proctitis	
	} bacterial with later possibility of allergic and psychogenic complicating factors
- C Psychogenic
 - 1—hysteria
 - 2—anal masturbation
 - 3—other psychoses
- D Traumatic

1—scratching	} mechanical
2—rubbing of clothing	
- E Allergic
 - 1—sensitization to bacterial toxins, fungi, or focal infections
 - 2—foods
 - 3—drugs, etc
 - 4—eczemas

- F Parasitic
 - 1—pinworms
 - 2—trichomonas
 - 3—monilia
 - 4—fungi
 - 5—itch mites
- G Thermal—warmth and associated perspiration (moisture)
- H Chemical
 - 1—chemical in diapers (washing) infant pruritus
 - 2—alkaline or acid urine
 - 3—self or prescribed medications
 - 4—sweat
 - 5—urine containing calcium or oxalate crystals
 - 6—urine of senile dribbling
- I General Metabolic
 - 1—thyroid dysfunction
 - 2—diabetes
 - 3—kidney disease
 - 4—liver disease
 - 5—anemia
 - 6—vitamin deficiencies
- J Reflex?

PHYSIOLOGY

It is important to consider the physiology of nerve tissue in order that we may properly interpret the therapeutic approach to a problem of pernicious eryptogenic pruritus ani. Nerve tissue is distinguished chiefly by its properties of excitability and a highly developed conductivity. Excitability is determined by the strength of stimulus required to initiate an impulse, while conductivity indicates the ability of the nerve fiber to transmit that impulse. The stimulus may be any chemical, electrical, mechanical or other external force.

It is important to note that the intensity of impulse in any nerve fiber is probably unrelated to the strength of the exciting stimulus. Thus, a fiber either responds with a maximum impulse or does not respond at all. Excitability varies from moment to moment and with the state of environment of the nerve fiber, but the all-or-none phenomenon functions at all times. Only a threshold stimulus, therefore, is required to produce an impulse.

In a consideration of irritated perianal nerve fibers we must realize that the threshold level of such fibers is, of necessity, much reduced. Thus, even a minimal stimulus will produce a response. Further, in accordance with the all-or-none response of nerve fiber, even this minimal stimulus, a slight irritation perhaps by clothing or perspiration, will produce a maximal nerve impulse, a markedly pruritic sensation.

When a nerve fiber is poisoned with a narcotic such as alcohol, or, as in the tattoo treatment, with mercuric sulphide (Cinnabar), the nervous impulse is diminished or completely extinguished in the poisoned area. But, after passing through such a region of im-

paired conduction and emerging into a normal nerve area the impulse resumes its normal higher level. This is in accord with the all-or-none phenomenon. The nerve fiber probably contributes the energy which keeps the impulse active and transmits it through normal nerve areas at a normal level.

Thus, if the perianal nerves are narcotized by an oil-soluble or other long-acting anesthetic, no stimulus will arouse an impulse in the treated nerves. However, as the narcosis begins to subside any stimulus that will pass the altering threshold will be transmitted at full intensity as soon as a non-narcotized nerve area is reached. At first the threshold level is high, and stimuli of minimal intensity that formerly produced a severe pruritic sensation cannot pass this threshold level. Only intense stimuli will do so. Gradually, however, as the anesthesia diminishes, lesser and lesser stimuli will pass the lowering threshold and produce a pruritic nerve impulse.

It is not known which of the cutaneous sensory end-organs conducts the sensation of pruritus. But whether it be the tactile corpuscles, the Pacinian corpuscles, the end bulbs of temperature or the free nerve ramifications of pain, the receptivity of that end-organ must be abolished for a prolonged period if we are to achieve clinical cure of that pruritus. Pruritic, traumatized skin must be put at rest. Only at rest will it repair itself.

Nature is kind. Given an opportunity it will restore diseased tissue to an approximation of normality. That opportunity is provided when we abolish the pruritic nerve impulses and put the injured tissue at rest. This may be accomplished by sedation or narcosis. This sedation may be local, general or both. Tattoo trauma acts to produce desquamation of pathologically altered tissue, and the mercuric sulphide functions primarily by poisoning the receptor end-organs and secondarily by local antiseptics. Nerve undercutting operations abolish pruritic impulses, provide the injured skin with healing time, and remove the necessity for vicious, self-inflicted scratch-trauma. Thus, all of these techniques act to put the diseased skin at rest. Natural powers of repair are then displayed by this unhampered skin at rest.

Obviously, then, it is clinically important to utilize as many measures as possible to achieve our goal. With this in mind I have devised the tattoo-neuotomy technique. It must be evident that although the mercuric sulphide remains permanently in the tissues of the tattooed area the sensory end-organs will eventually recover their conductivity. Further, we must expect a continuation of the pruritus in any microscopic skipped areas. Inasmuch as only a minimal recovery will permit stimuli to pass the altered threshold level, and inasmuch as a minimal stimulus may produce a maximal response (all-or-none phenomenon) it would be wise to further prolong the no-threshold level time by combining subcutaneous neuotomy with the tattoo. Thus the rationale of tattoo-neuotomy. It obviates

both microscopic skipped areas and recovery from poisoning

THERAPY

We will not here dwell upon the therapy of secondary pruritus ani. Where the causal factor is discovered it should, of course, be treated. We are here primarily concerned with cryptogenic pruritus ani. Nor will we discuss the treatment of mild cases by conservative measures such as ointments, injection of oil-soluble anesthetics, et cetera. Our discussion will be limited to the therapy of pernicious cryptogenic pruritus ani.

Let me preface my remarks by commenting upon

therapy may be employed without hospitalization, or at most, one or two days of hospitalization, and it is a controlled procedure. The operation of tattoo-neurotomy is equally ambulatory, and equally, if not more, effective.

The treatment of pruritus ani by tattoo was suggested by the observation that cutaneous secondary syphilides did not involve skin areas that had been previously tattooed red (ornamental designs) with mercuric sulphide (7). Since the mercurials are antiseptics as well as spirocheticides, tattoo of the pruritic perianal skin with mercuric sulphide was employed for

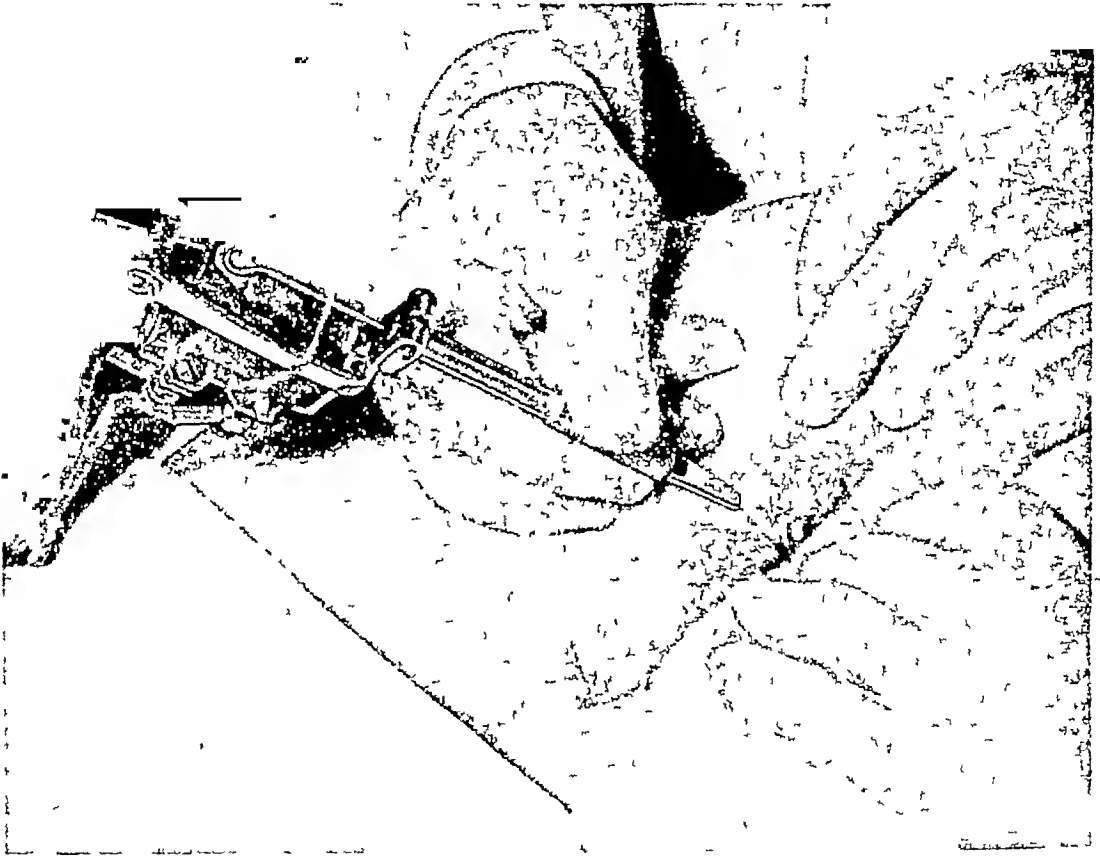


Fig 2 Note technique of holding the instrument, the 45 degree angle with the skin, straightening of perianal folds, and extent of tattoo

alcohol injection therapy. There is no doubt that if the pathological skin and nerve tissue is removed by sloughing there will be no pruritus during the period of primary nerve narcosis and the period of secondary tissue slough. The regenerated nerve and skin tissue, after this period of relative rest, will be definitely less susceptible to pruritic stimuli than the diseased tissue that it replaces. However, there can also be no doubt that any procedure involving sloughing, repeated abscess formation with its attendant incisions and drainages, and to an uncontrolled degree, is a non-surgical procedure. Further, this technique demands hospitalization in the average case for a period of six weeks, and sometimes longer. In comparison, tattoo

the antiseptic action. The therapy proved to be effective in a high percentage of cases. My own theory as to the physiology involved has already been discussed.

The tattoo instrument has a speed of about 3,000 vibrations per minute. The needle bar holds eight to ten needles, a number arbitrarily chosen to present a broad working surface. The needles are very fine, are set in a single row and are adjusted to penetrate to a depth of two millimeters.

The instrument is held with the shaft between the thumb, index and middle fingers, curving the ring and little fingers outward upon the patient's skin. The operator's elbow is held close to his body in order to

avoid tiring the forearm and to gain better instrument control. The needles must form a 45 degree angle with the skin. This is so that they will penetrate obliquely and will deposit the dye particles at the proper depth.

Dye penetration occurs chiefly with the stroke toward the direction of the needle points. Broad sweeps of tattoo are produced by a back and forth motion. Smaller areas are touched up by a small-circle rotary technique. Every perianal fold must be straightened and the skin kept under constant tension while tattooing. Skin tension may be maintained by the operator's left hand or by an assistant. It is important

tattooing, the needle points are dipped into the dye mixture.

Preparation of the patient is by shaving the perianal region, washing the area with tincture of green soap, and painting for antisepsis with iodine or tincture of metaphen followed by alcohol.

If the operation is to be performed in the office, local anesthesia is preferred. Oil soluble infiltration anesthesia is most suitable, for the prolonged post-operative anesthesia obviates post-tattoo discomfort. If hospitalization is deemed advisable a low spinal anesthesia, using 50 mg of procaine is best. This gives complete sphincter relaxation so that the tattoo may



Fig 3 Note incisions at borders of tattoo area, and hemostat under-cutting neurotomy

to avoid constantly maintaining the instrument in one position or one path, for ulceration may thus result. The entire perianal area must be carefully tattooed and the tattoo must be smooth and uniform. From time to time, while tattooing, the treatment area must be washed with a sponge dipped in sterile water or in alcohol, to determine the area of take. Bleeding, of course, must be constantly sponged.

The dye employed is mercuric sulphide (cinnabar). It is an insoluble red powder. A few cc of sterile distilled water, alcohol, solution of merthiolate or procaine, added to a small quantity of the dye will provide a suitable paste. Water alone is adequate. Added antiseptic or anesthetic action is obtained by employing the other solutions. From time to time, while

be easily carried beyond the anal verge into the anal canal.

Among the oil-soluble anesthetics should be mentioned Anucaine, containing in each 5 cc procaine base 0.05 gm, butesin, (n-butyl-p-amino-benzoate, Abbott) 0.20 gm, benzyl alcohol 0.25 gm, and sweet almond oil qs 5.00 gm. Rectocaine contains propyl amino benzoate, procaine base, and 5% benzyl alcohol in sesame oil. Gabriel's modified solution is oil of sweet almonds containing 0.5 per cent nupercaine, 1.0 per cent phenol and 10.0 per cent benzyl alcohol. Morgan's solution is peach kernel oil containing 1.5 per cent procaine, 6.0 per cent butesin, and 5.0 per cent benzyl alcohol. Another formula contains eucupin base 0.2 per cent, ethylaminobenzoate 3.0 per cent, benzyl

alcohol 50 per cent and oil of sweet almond q s

The anesthetic solution is warmed and then drawn into a twenty cc. Luer-Lok syringe with a two inch, twenty gauge needle. A primary procaine wheal is raised at the site through which the larger needle is to be inserted. Infiltration is slow and even, fanwise, subcutaneous, and may be started from anterior posterior and lateral points, injecting while withdrawing the needle. If the entire area is to be tattooed at one treatment the complete circumferential injection will require at least 20 cc of solution. The injection area must be thoroughly massaged to prevent pooling.

The perianal area is then coated with an ointment. Nupercainal, lanolin or carbolated vaseline may be employed. The ointment serves to hold the dye particles on the skin area during tattoo. Tattoo may then proceed as described (27, 28). It should be here emphasized that the tattoo must extend well beyond the pruritic zone for maximum effectiveness.

It will be recalled, from our discussion of physiology, that microscopic skipped areas and recovery from poisoning will reduce the percentage of cures. The combined tattoo-neurotomy technique was devised to obviate these two possibilities. Subcutaneous neurotomy alone will give a permanent cure in about seventy per cent of cases. Tattoo alone has proven effective in about ninety per cent of cases. In combination the percentage of cure is still higher. As yet there have been no failures but tattoo-neurotomy is too young a procedure to evaluate statistically. At present I employ tattoo-neurotomy to the exclusion of all other techniques in the therapy of pernicious cryptogenic pruritus ani (29).

When the tattoo is completed the entire area is repaired again by painting with an antiseptic dye and re-

draping. With a sharp knife a one-inch incision is carried through skin only, backward over the perineum from a point directly posterior to the anal verge. A similar incision is carried forward from a point anterior to the anal verge. Curved skin incisions are described, with their convexity laterally, for a length of one and one-half inches at each lateral margin of the tattoo area. A hemostat is then introduced through one of these curved incisions with its blades parallel to the skin surface and pointing toward the anterior midline incision. The skin is separated from the subcutaneous tissue by repeatedly opening the hemostat blades in this anterior quadrant until the blades issue freely through the anterior midline incision. The skin is elevated down to and including a small area of mucous membrane internal to the anal verge in each of the four quadrants by repeating the above procedure. This results in blunt severance of the subcutaneous nerves, a subcutaneous neurotomy. A tight pressure dressing completes the operation.

SUMMARY

A new classification for pruritus ani is suggested. Division into "secondary pruritus ani," when the etiology is discoverable, and "cryptogenic pruritus ani," for cases of undetermined etiology, would unify the literature and direct the practical therapeutic approach.

The etiology and physiology of the disease is discussed at length. The author's therapy of pernicious cryptogenic pruritus ani is described in detail. Tattoo with mercuric sulphide, and the operation of tattoo-neurotomy are recommended as the procedures of choice.

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The Effect of Dog's Bile, Certain Bile Acids and India Ink on Bilirubinemia and the Excretion of Bromsulfalein*

By

A. CANTAROW, M.D.

and

C. W. WIRTS, JR., M.D.†

PHILADELPHIA, PENNSYLVANIA

IN previous communications (1), we have described a procedure whereby the curve of elimination of bromsulfalein in the bile is determined simultaneously with the degree of its retention in the blood. Data obtained in human subjects and bile-fistula dogs support the hypothesis that a dual mechanism is involved in the removal of bromsulfalein from the organism. The first phase, i.e., its rapid removal from the blood, may possibly be largely a function of reticuloendothelial cell activity, while the second phase, i.e., its excretion in the bile, is probably a function of hepatic polygonal cell activity. The following criteria were established for normal excretion of the dye (1b): (a) no dye remains in the blood at the end of 30 minutes (2 mg. per kilogram dosage), (b) the dye usually appears in the bile during the first 15 minutes, attains a maximum concentration in 45-75 minutes, falling subsequently to a relatively low level at 2 hours, (c) 50-85% of the quantity of dye injected is excreted in the bile in the first hour and 65-100% in the first 2 hours.

This procedure has been employed in an investigation of the influence of administration of dog's bile (chiefly sodium taurocholate), sodium dehydrocholate and sodium deoxycholate and "reticuloendothelial blockade" with India Ink upon the excretion of bromsulfalein from the organism.

MATERIAL AND METHODS

Studies were made upon 4 cholecystectomized, bile fistula dogs, the bile draining externally. Bile was collected in 15 minute samples over a period of 2 hours after intravenous injection of 2 mg. of bromsulfalein per kilogram of body weight. Blood was withdrawn

from the femoral artery at the end of 30 minutes for estimation of the degree of dye retention and the serum bilirubin concentration (2). The concentration of bromsulfalein in the bile was determined by a method described elsewhere (1a), employing 0.1 cc. of bile, the final color reading being made with the Evelyn photoelectric colorimeter.

The studies were made under four different experimental conditions: (1) normal liver function and bile flow, (2) liver damage induced by carbon tetrachloride, (3) mild hepatic functional impairment immediately after operation (cholecystectomy and bile fistula), (4) incomplete bile stasis induced by partial occlusion of drainage tube. After a period of control observations under these conditions, the studies were repeated at intervals, as indicated in Tables 1-5, after administration of dog bile (150-200 cc.) by stomach tube, sodium dehydrocholate‡ (10 cc., 20% solution intravenously and sodium deoxycholate‡ (0.5 cc. per kilogram of a 10% solution in 0.9% NaCl) intravenously. These were administered usually at the time of injection of bromsulfalein. In some instances, indicated, sodium dehydrocholate was injected 2 hours before the dye. One dog received intravenous injections of India Ink (4 cc. Higgins' Ink in 16 cc. 0.9% NaCl) 1 hour before injection of bromsulfalein.

RESULTS

The data are presented in detail in Tables 1-5 and may be summarized as follows:

NORMAL LIVER FUNCTION AND BILE FLOW (Tables I and II)

Sodium Dehydrocholate. When given simultaneously with the bromsulfalein, the following phenomena

*We are indebted to Mr. Paul de Haen of Riedel-de Haen, Inc. for the sodium dehydrocholate (Decholin-Sodium) and sodium deoxycholate employed in this study.

*From the Departments of Medicine and Physiology, Jefferson Medical College and the Laboratory of Biochemistry, Jefferson Hospital.
†Ross V. Patterson, Fellow in Gastro-Enterology.
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curred (a) increase of about 200-500% in the 2-hour volume of bile, (b) decrease in the quantity of dye excreted to about 3-10% of the control excretion in 1 hour and to about 5-10% of the control excretion in 2 hours, (c) abnormal retention of dye in the blood, (d) increase in serum bilirubin concentration

When given 2 hours before injection of the brom-sulfalein, there was (a) no retention of dye in the blood, (b) no significant alteration in the volume of bile, (c) a questionable slight increase in serum bilirubin concentration, (d) a decrease in the quantity of dye excreted in the bile in 1 hour, but (e) normal dye excretion in 2 hours

Sodium Deoxycholate A slight degree of hemolysis occurred rather consistently, but no untoward reaction was observed. There was an increase in the 2-hour volume of bile (to 200%), with no significant alteration in dye excretion in the bile or retention in the blood and no increase in serum bilirubin concentration. *Whole Bile* There was a striking increase in the 2-hour bile volume (about 500%), with no abnormality of dye excretion in the bile or retention in the blood and no increase in serum bilirubin concentration.

India Ink (a) No significant alteration in 2-hour bile volume, (b) striking decrease in dye excretion in the bile, (c) retention of dye in the blood, (d) significant

TABLE I

Dog with normal liver function. Difference between effects of administration of bile, sodium dehydrocholate and sodium deoxycholate

Day of Experiment	Treatment	2 Hr Bile Volume cc.	Maximum Concentration Dye		Dye Recovery		Serum	
			mg. %	Mln	1 Hr %	2 Hr %	Dye %	Bilirubin mg. %
1		11.8	427	90	59	70	0	0.2
2		23.3	292	80	83	91	0	0.1
3		13.6	375	46	70	85	0	0.1
4	Sodium dehydrocholate	43.9	6	105	2	4	15	0.7
5		19	307	45	65	88	10	0.2
9		10.9	282	45	82	70	0	0.1
10	Sodium dehydrocholate	62.3	26	75	8	20	15	0.3
11		12.6	210	75	54	78	0	0.1
12		18.3	292	60	28	76	0	0.4
13	Sodium dehydrocholate 2 hours before	69.2	8	60	3	8	15	0.6
14		12.4	246	75	70	82	0	0.2
19		11.4	183	60	55	76	0	0.05
20	Sodium dehydrocholate 2 hours before	18.6	194	60	36	81	0	0.2
21		14.1	212	60	68	74	0	0.1
22		43	109	75	56	78	0	0.05
23	Sodium deoxycholate	81	46	75	58	82	0	0.1
24		12.2	226	60	61	82	0	0.1
25		72	10	105	5	83	0	0.4
26	Sodium deoxycholate	48	89	75	58	78	15	0.2
27		13.4	242	60	64	82	0	0.1

Bile 150-200 cc. by stomach tube at time of injection of dye.

Sodium dehydrocholate 10 cc. of a 20% solution intravenously with the dye unless otherwise specified.

Sodium deoxycholate 0.5 cc. per kg 10% solution in 0.9% NaCl at time of injection of dye

TABLE II

Dog with normal liver function. Effect of administration of India Ink (4 cc Higgins' Ink in 16 cc 0.9% NaCl) intravenously, 1 hour before injection of dye

Day of Experiment	Treatment	2 Hr Bile Volume cc.	Maximum Concentration Dye		Dye Recovery		Serum	
			mg. %	Mln	1 Hr %	2 Hr %	Dye %	Bilirubin mg. %
1		8.6	146	60	72	81	0	0.3
2	India Ink	14.8	134	60	12	19	20	0.3
3		14.3	128	45	23	47	0	0.05
4		20	38	60	14	33	15	0.3
5	India Ink	19.2	110	30	55	72	0	0.1
6		16	28	60	4	12	15	0.3
7		19.4	80	60	17	76	10	1.2
8	India Ink	16.2	138	90	8	36	30	0.9
9		21.4	115	75	10	40	25	0.7
10		11.8	186	60	41	62	0	0.2
12		10.9	174	60	64	78	0	0.1

increase in serum bilirubin concentration only after repeated daily injections

INCOMPLETE BILE STASIS

(Table III)

Sodium Dehydrocholate When given simultaneously with the bromsulfalein (a) increase of 100-300% in the 2-hour volume of bile; (b) increased excretion of dye in the bile, (c) increased retention of dye in the blood, (d) increase in serum bilirubin concentration (not with 2 cc dosage)

When given 2 hours before the bromsulfalein (a)

increase of about 100% in 2-hour bile volume, (b) increased excretion of dye in the bile, (c) no retention of dye in the blood, (d) increase in serum bilirubin concentration

Sodium Deoxycholate (a) Increase of about 100% in 2-hour bile volume, (b) increased excretion of dye in the bile, (c) no retention of dye in the blood, (d) no significant increase in serum bilirubin concentration

As reported previously (1b), with partial obstruction to the flow of bile excretion of dye in the bile diminishes some days before there is a demonstrable

TABLE III

Dog with incomplete bile stasis due to partial obstruction of drainage tube Effects of administration of sodium dehydrocholate and sodium deoxycholate as indicated in Table I

Day of Experiment	Treatment	2 Hr Bile Volume cc	Maximum Concentration Dye		Dye Recovery		Serum	
			mg %	Min	1 Hr %	2 Hr %	Dye %	Bilirubin mg %
1		0.4	264	45	72	81	0	0.1
2		0.4	182	50	46	68	0	0.1
3		6.2	46	90	20	44	0	0.3
4		4.6	44	105	20	71	0	0.5
5		3.9	42	120	2	18	5	0.7
6	Sodium dehydrocholate	18.4	137	90	27	38	15	0.9
7		6.0	188	120	4	14	0	0.5
8	Sodium dehydrocholate 2 hours before	15.4	233	75	20	62	0	0.0
9		6.4	218	105	1	16	5	0.7
10	Sodium dehydrocholate 2 cc	12.4	200	90	16	30	10	0.4
11		6.9	147	105	6	18	0	0.5
12	Sodium deoxycholate	14.8	164	60	21	45	0	0.8
13		5.8	75	90	5	21	0	0.8

TABLE IV

Impaired liver function due to CCl₄ Effects of administration of bile, sodium dehydrocholate and sodium deoxycholate

Day of Experiment	Treatment	2 Hr Bile Volume cc	Maximum Concentration Dye		Dye Recovery		Serum	
			mg %	Min	1 Hr %	2 Hr %	Dye %	Bilirubin mg %
1 33	8 cc CCl ₄ every 4 days							
36		4.1	180	105	2	16	5	0.4
37		6	238	105	2	19	10	0.5
38		7	110	105	2	12	20	0.3
39		6.8	230	45	13	24	10	0.5
40	Bile	44.8	13	45	15	22	15	0.1
41		9.2	98	45	9	15	20	0.2
42	8 cc CCl ₄							
43		6	8	105	0	0.1	40	0.2
44		7.6	9	75	0.3	1	100	0.8
46	Sodium dehydrocholate	11.5	18	90	1	3	40	0.6
47		8.2	62	75	2	7	30	0.4
49		13.4	68	45	10	17	15	0.2
50	Sodium deoxycholate	14.2	34	60	12	20	0	0.1
50	8 cc CCl ₄							
51		7.2	45	90	0	7	15	0.2
52	Sodium dehydrocholate	32.4	6	60	2	5	40	0.5
53		6.8	16	105	3	8	20	0.3
54	Sodium deoxycholate	18.8	22	105	4	10	15	0.3
56		7.4	34	90	11	20	15	0.4
57	Bile	42	28	75	15	24	15	0.4

CCl₄ given by stomach tube Bile sodium dehydrocholate and sodium deoxycholate as indicated in Table I

increase in the serum bilirubin concentration or 30-minute retention of dye in the blood

HEPATIC DAMAGE DUE TO CARBON TETRACHLORIDE (Table IV)

24-48 hours after administration of a toxic dose of carbon tetrachloride there occurred consistently (complete data not in table) (a) a decrease in the volume of bile, (b) marked decrease in the excretion of dye in the bile, most pronounced in the first hour, (c) comparatively slight retention of dye in the blood and (d) slight increase in serum bilirubin concentration. Improvement was noted at 48-72 hours. The data in Table IV constitute the findings after prolonged administration of carbon tetrachloride.

Sodium Dehydrocholate When given simultaneously with the bromsulfalein (a) moderate increase in 2-hour bile volume, (b) no significant decrease in excretion of dye in the bile, (c) questionable increase in retention of dye in the blood, (d) questionable increase in serum bilirubin concentration.

When given 2 hours before injection of bromsulfalein slight increase in 2-hour bile volume, with no increase in serum bilirubin concentration or retention of dye in the blood.

Sodium Deoxycholate Variable, slight increase in 2-hour bile volume, with no significant effect on excretion of dye in the bile, serum bilirubin concentration or retention of dye in the blood.

Whole Bile Striking increase (about 500%) in 2-hour bile volume, with no significant change in excretion of dye in the bile, serum bilirubin concentration or retention of dye in the blood.

SPONTANEOUS POST-OPERATIVE IMPAIRMENT OF LIVER FUNCTION (Table V)

Sodium Dehydrocholate (a) Marked increase in 2-hour bile volume, (b) marked decrease in excretion of dye in bile, (c) increased retention of dye in blood, (d) increase in serum bilirubin concentration (except when bile had been given on the previous day).

Whole Bile (a) Striking increase in 2-hour bile

volume, (b) increased excretion of dye in bile, (c) no significant increase in serum bilirubin concentration or in retention of dye in blood.

COMMENT

It has been known for some time that choleresis induced by dehydrocholic acid is largely hydrocholeresis, i.e., an increased output of water with a decreased concentration of solids. Interest has centered chiefly in the effect of this agent on the excretion of cholic acid, which appears to be variable (3, 4, 5, 6, 7). Berman et al (4) found a consistent decrease in the 24-hour biliary excretion of cholesterol following oral administration of 3-5 Gm of dehydrocholic acid, there was no consistent alteration in the total excretion of bile pigment. Other bile acids rather consistently increased the output of cholesterol in the bile. Increased bilirubinuria was observed by Adler et al (8) in jaundiced subjects following intravenous injection of sodium dehydrocholate, and Wespi (9) reported that this agent caused more rapid removal of intravenously injected bilirubin from the blood stream and increased bilirubinuria in rabbits. On the other hand, Marengo and Massimello (10) and Pass (11) have observed an increase in serum bilirubin concentration after administration of sodium dehydrocholate. Mills and Dragstedt (12) found that it had little or no effect on the rate of removal of intravenously injected bilirubin from the blood stream (dogs), but observed a significant delay in the rate of removal of bromsulfalein, injected 5 minutes after the dehydrocholate (25 and 5 cc, 20% solution).

The effects of sodium dehydrocholate in the present study differed strikingly from those of whole dog's bile (chiefly sodium taurocholate) or sodium deoxycholate when given to normal bile-fistula dogs in quantities that produced comparable increases in the 2-hour bile volume. During the period of choleresis produced by the former there was an elevation of serum bilirubin concentration, delay in the removal of bromsulfalein from the blood and marked depression of its excretion in the bile. These phenomena were not observed during choleresis following administration of either

TABLE V

Dog with mild impairment of liver function following operation. Effects of administration of bile and sodium dehydrocholate, as indicated in Table I.

Day of Experiment	Treatment	2 Hr Bile Volume cc	Maximum Concentration Dye		Dye Recovery		Serum	
			mg %	Mln.	1 Hr %	2 Hr %	Dye %	Bilirubin mg %
1		10.3	285	60	20	48	0	0.1
2	Bile	81	37	60	33	54	0	0.1
7		18.2	122	75	9	38	0	0.1
8	Bile	47.4	62	60	41	57	0	0.1
10	Sodium dehydrocholate	64	2	75	1	3	40	1.7
12	Sodium dehydrocholate	74	1	48	3	4	30	1.3
13	Bile	78.4	34	60	33	55	10	0.5
14	Sodium dehydrocholate	62.4	14	48	20	27	20	0.5
16		13.2	45	45	23	48	0	0.6

whole bile or deoxycholate. These effects of sodium dehydrocholate appeared to be related to its choleric effect, inasmuch as no increase in serum bilirubin concentration or 30-minute dye retention was noted after 2 hours and the delay in excretion of dye in the bile persisted for only 3 hours. It is possible that studies of the degree of 5-minute retention of bromsulfalein in the blood might have revealed the persistence of abnormality for a longer period.

It is apparent that the state of hepatic and biliary tract function influence to a remarkable degree the consequence of administration of these agents. In the presence of mild post-operative spontaneous impairment of liver function, sodium dehydrocholate produces essentially the same effects as in normal animals (i.e., cholemesis, bromsulfalein and bilirubin retention in the blood and impaired dye excretion in the bile), whereas whole bile caused an increase in the rate of excretion of dye in the bile simultaneously with an increase in the 2-hour bile volume. In the case of hepatic damage due to carbon tetrachloride, however, although a marked increase in 2-hour bile volume followed administration of whole bile and a moderate increase followed dehydrocholate, neither these agents nor deoxycholate had any significant effect upon the degree of bilirubinemia or dye retention or upon the rate of excretion of dye in the bile. The reason for these divergent findings in these two types of hepatic functional impairment is not clear. It may be due merely to a difference in the severity of hepatocellular damage, but it may possibly be related to the occurrence of impairment of function of the Kupffer cells in addition to that of polygonal cells in carbon tetrachloride poisoning (13).

The findings following administration of dehydrocholate in the presence of partial bile stasis differed strikingly from those obtained with this agent under other conditions, in that moderate cholemesis, increased bilirubinemia and retention of bromsulfalein in the blood were accompanied by a striking increase in the concentration and rate of excretion of the dye in the bile. This acceleration of dye excretion in the bile was more pronounced during the second to fourth hours, cholemesis persisting during this period, in contrast to its earlier subsidence in normal animals. On the basis of these observations, two conclusions are suggested:

(a) The rate of excretion of bromsulfalein in the bile may be influenced independently of the rate of its removal from the blood, this was also suggested by previous findings in partial bile stasis (1b). (b) Whereas, under otherwise normal conditions of bile flow cholemesis induced by dehydrocholate is accompanied by inhibition of excretion of bromsulfalein in the bile, the relationship is probably not one of cause and effect, the two phenomena being perhaps due to a common cause which does not operate in the same manner under conditions of partial bile stasis. Adlersberg and Neubauer (14) believed that dehydrocholic acid is excreted preferentially in the bile, decreasing

the concentration of other bile constituents. This does not appear to be necessarily the case under abnormal conditions.

The findings obtained after injection of India Ink are in accord with those of other investigators (12, 15, 16, 17, 18), which suggest that cells of the reticuloendothelial system play an important part in the removal of halogenated phthaleins from the blood stream. Whether or not the decreased rate of elimination of the dye in the bile is secondary to interference with reticuloendothelial cell function caused by India Ink cannot be stated on the basis of available data. The observation of Yonemura (19) is also corroborated that administration of India Ink has no significant influence upon the volume of bile.

SUMMARY

Cholemesis following intravenous injection of sodium dehydrocholate in a normal bile-fistula dog was accompanied by (a) increase in serum bilirubin concentration, (b) delayed removal of bromsulfalein from the blood and (c) diminished rate of excretion of bromsulfalein in the bile. These effects were not observed 2-3 hours after injection and did not accompany the increased flow of bile induced by administration of dog's bile or sodium deoxycholate. The same phenomena followed administration of dehydrocholate to a dog with a mild degree of spontaneous post-operative impairment of liver function. In this dog, excretion of bromsulfalein in the bile was increased by oral administration of whole bile.

In a bile-fistula dog with severe impairment of liver function induced by carbon tetrachloride, the 2-hour bile volume increased moderately after administration of whole bile and dehydrocholate, but neither these agents nor sodium deoxycholate had any significant influence upon the level of serum bilirubin, the degree of retention of bromsulfalein in the blood or the rate of excretion of dye in the bile.

In the presence of partial bile stasis, administration of sodium dehydrocholate was followed by (a) moderate cholemesis, (b) increase in serum bilirubin concentration and (c) delayed removal of bromsulfalein from the blood, but, in sharp contrast to the findings in normal animals, there was (d) a simultaneous increase in the rate of excretion of dye in the bile. These effects, with the exception of dye retention in the blood, were also observed during the second 2-hour period after injection of dehydrocholate. Excretion of dye in the bile was also increased after injection of sodium deoxycholate in the presence of partial bile stasis. The possible significance of these observations is discussed.

Intravenous injection of India Ink was followed by an increase in serum bilirubin concentration, delayed removal of bromsulfalein from the blood and diminished rate of excretion of dye in the bile, with no significant alteration in the 2-hour bile volume.

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Some Effects of High Fat Diets on Intestinal Elimination. 1

By

HELEN L WIKOFF, Ph D, SAMUEL D KOONCE MS†

and

H JANE MCGUIRE, MS‡

COLUMBUS OHIO

IN a recent investigation conducted in this Department (1), human subjects were put on diets containing large amounts of fried foods pastries and other fat-rich foods. Several of the individuals who participated in the experiment noticed intestinal effects as a result of the diet. Some of these persons experienced diarrhea and others were constipated.

Because of the conflicting nature of these symptoms, a thorough search of the literature was made to learn what had been reported with regard to the effects of high fat diets on intestinal elimination. Chief work found was that of Mrs F H Smith (2), of the Mayo Clinic who introduced a high fat diet for the treatment

of constipation. The fatty foods used in large quantities by Mrs Smith were cream, butter and marmalade (85% fat). McLester (3) commenting on the Mayo diet, states that too much fat will cause diarrhea or perhaps diarrhea alternating with spastic constipation, but gives no clinical evidence in support of his claim. He prohibits the use of fatty or greasy foods in the treatment of an irritable colon (4). The late Dr Bridges also recognized that the Mayo diet had merit in some cases, but stated that in his experience those patients able to tolerate a diet high in fat were in the minority. For the treatment of constipation (5) he advised the omission of fried foods, pastries, and other fat-rich foods such as were included in the diets which gave rise to the contradictory symptoms in the persons participating in the experiments conducted in this Department.

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†Comby Research Fellow in Physiological Chemistry The Ohio State University 1939-1940.

‡Comby Research Fellow in Physiological Chemistry The Ohio State University 1940-1941.

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For many years, it has been assumed that the formation of insoluble soaps in the intestine is a factor in the production of constipation. Bosworth, Bowditch and Giblin (6), in a study of infant diets, found that the formation of insoluble soaps was due to the calcium content of ingested milk. On the other hand Telfer (7), in a study of adult diets, found the formation of soaps was correlated with the presence of a large excess of fatty acids in the intestine. Both he and Zucker (8) also noted that the acid-base balance of the body determined the extent of calcium excretion in the feces.

These rather meager data do not explain to our satisfaction why some subjects experienced diarrhea, others constipation, and still others were not affected at all when the same heavy fat diet was eaten by all who participated in the experiment described above. Some physicians claim that constipation is a subjective symptom in humans and may be brought about by the patient himself, while diarrhea is an objective symptom beyond the control of the patient. However, no such claim is made in the case of animals.

Because white rats thrive on relatively unvaried diets, it was decided to conduct some feeding experiments in which increasing amounts of various fats were to be added to an adequate basic rat diet. The production of either constipation or diarrhea in these animals would not be subject to their mental condition and collection of the total amount of feces excreted could be easily managed for fat analyses.

PROCEDURE

Two groups of five rats each, one consisting of five females, the other of five males, were fed the experimental diets. Whenever possible, litter mates were selected for the groups, otherwise, rats of approximately the same age were used. Only those rats which appeared to be normal in every respect were placed on the experimental diets while their appearance and behavior was carefully watched throughout the experiment. Aside from variations in diet, the entire colony of rats used was subjected to the same conditions.

The experimental diets were prepared from Purina Laboratory Chow* large checkers, a standard animal

*Chemical analysis — Purina Dog Chow

	% Crude	% Digestible	Mineral Analysis
Protein	23.0	19.0	Fe 0.018 Mg 0.09 SiO ₂ 0.28 K 0.56 Na 0.67 Cl 0.68 P 1.17 Ca 2.22
Fat	5.0	4.7	
Fiber	4.0		
Ash	7.0		
Nitrogen free Extract	54.0	48.0	l Enough not to be Ca/P 1.9 to 1
Moisture	7.0		
	100.0	71.7	

Vitamin Content

A — about 400 International Units/lb

B — about 275 Sherman Units

C — low

D — about 500 International Units

F — no measurement but supplied by wheat germ

G — 300 Sherman Units/lb

Fuel value per pound—1400 calories

food designed to provide the animal with a well-balanced diet. This material fed to all of the control animals and to the experimental animals when not on special diets, was consumed at a rate of approximately 0.90 pounds per month per adult rat.

In the preparation of special diets, the Purina Laboratory Chow was ground to a fine powder in a power mill, a small quantity of water then added to the powder and the whole mass thoroughly mixed in a large mortar. The fatty oil or fat (melted on a water bath) was next added slowly to this material with constant stirring. The resulting mixture, after being thoroughly homogenized both with a pestle and by hand, resembled a stiff dough which was spread in pans and cut into small pieces resembling the original checkers. In order to prevent mold formation on the food, the pans were placed in a refrigerator where, after a few hours, the dough became stiff and brittle resembling the texture of the original checkers. The weights of oil or fat and the weight of dry powder were carefully measured before mixing to insure the proper percentage of fat in the mix.

While the rats were being fed the experimental diets they were kept in individual metabolism cages with false wire mesh bottoms to facilitate collection of feces and to prevent contamination of feces with food. The feces accumulating during the first forty-eight hours after the initiation of a special diet were always weighed and discarded. Feeding of the special diet was continued for one week during which time the total amounts of feces eliminated were collected separately from each cage and weighed.

The weights of the animals used in the experiments were also carefully noted, both immediately before and at the conclusion of a special diet. As soon as a test feeding period was ended, the animal was fed the standard diet for at least one week before being fed another test fat.

Before analyses were made, the feces were separated from foreign particles, such as food or hair, and were ground without drying in a mortar to a homogeneous mass, sometimes pulpy, sometimes powdery.

In order that all fat determinations might be reported on a dry basis, moisture determinations were made by drying the ground material to constant weight in an oven at 110° C, approximately 120 hours being required. For the actual fat determinations, neutral and acidulated* ether extracts of the ground material were made. Since the work of Saxon (9), as well as that of Fowweather (10), has shown that more accurate results are obtained by wet methods, the material to be extracted was not previously dried.

The extractions were made in the ordinary type of Soxhlet apparatus of Pyrex glass, fitted throughout with ground glass joints. Thimbles of size 43 x 123 mm were used, the samples being carefully wrapped in filter paper in addition to the use of a plug of cotton in the thimble to prevent the mechanical loss of particles. The extractors were protected from the

*0.1 N solution of dry HCl gas in anhydrous ether

atmosphere by calcium chloride drying tubes attached to the end of the reflux condensers. Thirty hours were found to be the optimum period for complete extraction of the lipids.

The ether extracts contained considerable amounts of dark colored water soluble material. Purification was effected by evaporating the ether and extracting the residues with petroleum ether for six to eight hours at from 30-60° C., a modification of the method of Hill and Bloor (11). The weights of purified materials were then determined.

Present in the material obtained by extraction with neutral ether were neutral fats, fatty acids and unsaponifiable matter. The acid ether extract consisted of the fatty acids originally present in soaps in addition to the substances found in the neutral ether extract. Extracts made with acid ether after previous removal of the neutral fats, fatty acids and unsaponifiable matter with neutral ether, contained the fatty acids from the soaps. As a check against this value, the difference between the values for the total acid ether extracts and the neutral ether extracts could also be used as a measure of the fatty acids held as insoluble soaps.

Iodine numbers of all purified extracts (neutral ether and ether and soaps) were determined by the Wijs method.

DISCUSSION AND RESULTS

Because lard had been the lipid which had produced most of the erratic results (with respect to intestinal elimination) in the case of humans eating high fat diets, lard was the first fat added to the standard diets fed to the albino rats. Observations were made when diets containing five, ten, fifteen and twenty per cent added lard were fed. However, in no case was either diarrhea or constipation produced in the rat.

Analyses of the feces revealed small but gradually increasing amounts of fats present as the lard content of the rat diet was increased (Table I). Soaps likewise increased with the fat content of the diet. Iodine numbers of the soaps formed were much less in every case than for the corresponding total fat extracts indicating a greater tendency for the formation of saturated soaps than for the formation of unsaturated soaps.

Since none of the rats had experienced either diarrhea or constipation after eating diets rich in lard several other diets each containing ten per cent of the added fat or oil were fed. Included among these materials were ordinary edible fats or oils such as olive oil, corn oil, cottonseed oil and Crisco. However the rats raised no particular objection to other added fats and oils such as cocoa butter, bayberry tallow, menhaden and linseed oil which are not ordinarily regarded as articles of the American diet.

With the exception of the diets containing ten per cent added cocoa butter or ten per cent added bayberry tallow, none caused any unusual effect on intestinal elimination in the rat. Similar results followed when twenty per cent of the various fats were added to the diets. Marked constipation with clay colored stools was produced by the addition of either ten or twenty per cent bayberry tallow or cocoa butter to the diet. Added olive oil, cottonseed oil, corn oil, Crisco or even linseed oil did not affect elimination in the rat.

As soon as the high fat diets had produced diarrhea in our rats, we began to suspect that the intestine of a rat might react differently toward fat than the intestine of a human. We therefore administered 2 cc. doses of castor oil by stomach tube to a group of rats but were unable to produce diarrhea or even a mild laxative effect. Similar results were obtained when 2 cc. doses of the fatty oils listed in Table II were given by stomach tube to rats. Since the dose of castor oil administered to the rats was at least a hundred times the dose given to humans (based on body weight), it seems reasonable to conclude that the intestines of rats do not react toward fatty oils in the same manner as the intestines of humans.

In the two instances where constipation resulted (bayberry tallow and cocoa butter) the quantity of soaps present in the feces was much greater than after feeding the standard control diet (Table II) or the other test fats. That these soaps consisted principally of saturated material was shown by the low iodine numbers. Because the iodine numbers of bayberry tallow (19) and cocoa butter (38.7) were lower than the iodine number of any of the other fats fed it occurred to us that the presence of saturated acids in the fat might be responsible for the production of constipation.

TABLE I

Quantities and iodine numbers of the fat extracted from feces of albino rats fed lard in measured quantities

	Fat Extracted				Added Lard	Iodine Numbers		
	Neutral Ether	Acid Ether	Soap by Difference	Soap Direct Extraction		Neutral Ether	Acid Ether	Soap Extract
Control	2.7	1.0	0.3	0.7	—	41.6	72.9	15.5
5% Lard	2.4	3.6	1.2	1.2	7.4	75.1	61.3	35.4
10% Lard	3.7	4.0	0.3	1.1	7.4	61.8	79.6	33.6
15% Lard	3.3	6.2	2.9	2.7	7.4	71.1	48.8	53.0
20% Lard	5.1	10.3	5.2	4.0	7.4	55.3	34.1	27.8

(Ten rats, five males and five females were used in each of the above feeding experiments and the values given in the table represent the average values obtained for the group.)

Since we had some tributyrin on hand, feedings of the standard diet with five, ten, fifteen and twenty per cent added tributyrin were next made. However, in no instance was the intestinal elimination of the rats affected. The fat content of the feces, during the feeding of added tributyrin was also similar to that of the control period (Table III).

From these data, it appears that the feeding of satu-

rated fats does not necessarily result in the production of constipation in rats.

Since no special search of the literature had been made at the time tributyrin was fed, we were unaware that Eckstein (12) had been unable to feed the compound to rats used in metabolism studies. According to his statement, the rats disliked the bitter taste of tributyrin and they refused to eat diets consisting of

TABLE II

Quantities and iodine numbers of fat extracted from feces of rats fed diets containing ten and twenty per cent added fats

Diet	% Fat Extracted				Iodine Numbers			
	Neutral Ether	Acid Ether	Soap by Difference	Soap by Extraction	Ingested Fat	Neutral Fat Extract	Acid Ether Extract	Soap Extract
Control	3.8	4.8	1.0	0.8	—	67.2	50.2	37.6
10% olive oil	4.2	5.8	1.6	.7	82.7	68.3	45.0	37.4
20% olive oil	6.4	5.9	2.5	1.9	82.7	65.9	53.5	32.1
Control	2.5	3.2	0.7	—	—	82.3	66.1	—
10% corn oil	4.1	4.7	0.6	—	160.0	64.0	52.4	—
20% corn oil	5.4	6.0	0.6	—	160.0	102.0	92.0	—
Control	2.7	3.0	0.3	0.6	—	81.6	72.0	35.5
10% lard	3.2	4.0	0.8	1.1	79.4	61.8	59.6	33.4
20% lard	5.1	10.3	5.2	4.0	79.4	55.3	39.1	27.8
Control	1.9	2.9	1.1	2.0	—	84.0	54.8	47.5
10% Crisco	13.1	16.3	3.2	3.1	103.0	59.4	60.4	32.4
20% Crisco	14.9	15.7	3.8	3.7	103.0	44.8	34.3	22.6
Control	2.1	4.4	2.3	.51	—	45.1	36.3	—
10% linseed oil	3.9	5.2	1.3	.55	165.0	80.8	81.6	—
20% linseed oil	5.1	7.2	2.1	1.25	165.0	96.8	87.2	34.1
Control	3.2	4.0	.8	1.1	—	78.9	61.8	—
10% cocoa butter	4.1	19.2	14.1	8.1	38.3	66.3	25.0	7.8
20% cocoa butter	17.1	27.8	10.7	19.1	38.3	32.2	22.6	8.0
Control	4.51	5.18	.67	1.51	—	67.63	62.34	40.15
10% cottonseed oil	7.25	8.37	1.12	1.86	100	60.30	54.29	49.12
20% cottonseed oil	7.38	10.42	3.04	5.00	100	63.85	54.58	57.20
Control	7.66	8.77	1.11	1.19	—	64.1	53.2	29.5
10% menhaden oil	9.46	11.53	1.07	1.22	154	96.6	56.4	38.6
20% menhaden oil	11.92	17.14	5.49	3.28	154	73.2	48.8	25.7
Control	4.28	5.64	1.36	2.04	—	55.8	48.0	17.9
10% bayberry tallow	5.89	21.51	15.62	14.23	1.9	46.1	15.7	10.8
20% bayberry tallow	7.07	27.08	20.91	21.43	1.9	38.5	12.6	16.4

TABLE III

Quantities and iodine numbers of the fat extracted from feces of albino rats fed tributyrin in measured quantities

	% Fat Extracted				Iodine Numbers			
	Neutral Ether	Acid Ether	Soap by Difference	Soap by Extraction	Added Tributyrin	Neutral Ether	Acid Ether	Soap Extract
Control	6.60	6.92	0.23	0.92	—	47.3	64.2	48.6
5% Tributyrin	7.14	7.37	.23	0.95	0.6	49.2	52.7	51.7
10% Tributyrin	7.44	7.63	.19	1.06	0.6	43.7	50.1	46.4
15% Tributyrin	6.59	6.98	.39	1.29	0.6	48.5	45.9	52.4
20% Tributyrin	5.94	6.42	.45	1.15	0.6	59.6	52.2	46.2

5% tributyrin added to a mixture of vegetable, salt mixture, casein, gelatin and starch Davis (13) fed rats diets containing approximately 9% tributyrin added to mixtures of lard, starch, casein, yeast, salt mixture and ground paper Despite the fact that his experiments were run for about three weeks and no ill effects recorded, Davis nevertheless claimed tributyrin to be toxic to rats because the intraperitoneal injection of 10 cc killed the rat within an hour Although these experiments have no direct bearing on our work, it should be noted that our rats relished their diets, even when 20% tributyrin was added Furthermore, no toxicity of any kind was apparent

SUMMARY

1 Measured amounts of test fats mixed with a standard rat food (Purina Chow Checkers) were fed to white rats in order to see whether intestinal elimination would be affected by the added fat

2 Ten and twenty per cent additions of lard, cottonseed oil, olive oil, linseed oil, menhaden oil, Crisco, bayberry tallow, cocoa butter or tributyrin to the standard rat food were the combinations fed

3 From the rat feces collected during the feeding experiments, the following three fractions were separated Total lipid content, soap fat, lipid content other than soap fat Iodine numbers were run on each of the fractions

4 Constipation resulted from feeding the rats mixtures of standard rat food with cocoa butter and with the bayberry tallow, in both ten and twenty per cent levels

5 More soap was present in the feces following the diets which had produced constipation than in any other cases

6 The added fats which caused constipation (cocoa butter and bayberry tallow) had lower iodine numbers than the other fats fed The only exception was tributyrin, which had no effect on elimination and had practically no iodine number The iodine numbers of the soaps isolated from the feces of the constipated animals were much lower than in any other case

7 None of the other fats fed produced any effects on intestinal elimination in the rats Diarrhea could not be produced by feeding fats to rats, no laxative action was noted even when 2 cc doses of castor oil were given by stomach tube

8 Diets consisting of twenty per cent tributyrin added to standard rat food were relished by rats, although previous investigators have reported tributyrin as toxic and so distasteful that rats refused to eat concentrations of as low as 5% tributyrin added to a standard rat food

CONCLUSIONS

Although these experiments do not show to our satisfaction why people eating high fat diets experienced a variety of intestinal results, we have shown that constipation can be produced in a rat fed certain types of fat. However, rats are unsuitable for studies of the possible production of diarrhea by high fat diets since castor oil itself is shown to have no laxative action on the rat.

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Cardiospasm: Successful Treatment by Esophagogastrostomy*

By

JACOB LICHSTEIN†
PHILADELPHIA, PENNSYLVANIA

INTRODUCTION

IT is generally agreed that the medical treatment of cardiospasm is effective in two-thirds of all cases when complete dilatation of the cardia is adequately accomplished. However, since fully one-third of all cases do not respond to conservative therapy, surgical intervention must at one time or another be considered. Contrary to general opinion, statistics on the operative risk show only a slightly lower mortality than that which prevails when large groups of patients are treated without any recourse to radical measures (1).

Great studies have been made in recent years in the surgical approach to the therapy of cardiospasm. Esophagogastrostomy as an attempt to relieve the symptoms by short-circuiting the cardia has evolved as the end result of a succession of operations over the years. To the ninety-nine cases collected by Ochsner (1) thus operated upon, two of which cases he performed, we herewith add a report of the successful use of esophagogastrostomy in a case of long-standing achalasia in which all other methods after thorough trial produced no results.

ETIOLOGY OF CARDIOSPASM

A consideration of the possible etiologic factors involved is necessary for an adequate appraisal of the attempts at treatment of this interesting condition. One of the earliest concepts was proposed by Einhorn and Rolleston (2). They believed that cardiospasm was due to failure of the cardia to relax rather than actual spasm. This was considered due to inhibition of the contraction of the longitudinal muscle fibers. For this reason, the term "achalasia" has found its place in the literature.

The "pinchcock" theory advanced by Jackson (3) conceives of the diaphragmatic musculature acting upon the hiatal opening so as to pinch the esophagus much as a pinchcock closes the rubber tubing of a buret. He ascribes the disorder to the incoordinate failure of the diaphragmatic pinchcock to open normally in the cycle of deglutition without the necessary presence of spasm. On this basis, he prefers the term "preventriculosis."

Vinson (4) is of the opinion that cardiospasm is a disturbance of the nerve-muscle mechanism of the esophagus and cardia produced by degenerative changes in the vagal nerve supply resulting in overaction of the sympathetic fibres.

Evidence is presented by Eduardo Etzel (5) from a

clinical experience of 170 cases favoring the thesis that this disease complex is caused by a chronic or intermittent Vitamin B₁ deficiency and is a manifestation of a degenerative disease of the autonomic intramural nervous system.

Experimental and clinical evidence accumulated in recent years points to the disturbance as being one due to degenerative changes involving the ganglion cells of the plexus of Auerbach (6). Landrum in studying a series of cases of cardiospasm microscopically found no evidence of hypertrophy of the cardiac sphincter but in all cases observed a marked loss or complete absence of the ganglion cells of the myenteric plexus (7).

According to Knight, experimental bilateral vagal section reproduced in cats the clinical and pathological picture of achalasia and on this basis he advocated the use of sympathectomy as a therapeutic procedure (8, 9). In the human, he showed that the sympathetic supply to the cardiac sphincter derives from the left side of the celiac plexus and was distributed along the left gastric artery. Consequently, the excision of this artery and the surrounding fat and nervous tissue has been advocated as one form of surgical treatment.

These successive theories of the possible etiologic factors find expression in the current medical and surgical approaches in treatment.

HISTORICAL REVIEW OF SURGICAL APPROACH TO THERAPY OF CARDIOSPASM

A number of methods have been employed in the surgical treatment of achalasia. They have fallen into four great groups. Operations directed at the dilated esophagus, at the diaphragm, at the nerve supply of the esophagus and at the cardia (1).

Operations directed at the dilated esophagus such as excision of the portions of the wall and esophagoplication (suturing of the longitudinal folds of the esophageal wall) is of purely historical interest. Those directed at the diaphragm in which division of the diaphragmatic crura was attempted with the view of overcoming the supposed failure of relaxation of the crura have met with consistently poor results. Operations on the nerve supply, namely vagotomy and sympathectomy, have been attempted following extensive experimental observations. Vagotomy, first performed in 1911, proved almost uniformly unsatisfactory and has at present been abandoned.

Sympathectomy in the treatment of achalasia has found greater favor since the experimental work of Knight (8, 9) who relieved the condition in cats by this procedure. He performed the operation with some

*From the Jewish Hospital, Philadelphia, Pennsylvania.
†First Lieutenant, Medical Corps, U. S. Army.
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Fig 1 Flat chest roentgenogram in patient with a 20 year productive cough pain in back and mild dysphagia. Large circumscribed shadow occupying one third of chest is seen November, 1937

success in humans by exercising the sympathetic supply to the cardiac sphincter distributed along the left side of the celiac plexus and the left gastric artery. Subsequent reports of the use of this procedure by other operators leave the beneficial results of sympathectomy as an effective means of correcting the disturbance of the nervous mechanism still to be weighed in the balance.

Esophagogastrostomy, as an attempt to relieve the symptoms by short-circuiting the cardia has emerged at present as the culmination of a succession of operations about the cardia. These began with retrograde dilatations and stretching of the cardia in 1903 by Mikulicz. Good results were reported in 70.8% with deaths in 8.9%. This was superseded by the operation of extramucous cardiomyotomy and later by cardioplasty. Excision of the cardia followed by esophagogastrostomy was first performed in 1920 by Bier in a case reported by Pribam (10).

The procedure of esophagogastrostomy without cardiectomy is the soundest surgical approach according to Ochsner, he recommends a side-to-side anastomosis between the esophagus and stomach thus side-tracking the cardia or preferably an operation in a manner similar to a Finney pyloroplasty in which the presence of a spur is obliterated. In the 99 cases he has collected from the literature are included 9 cases

reported by Wachs in which 5 died, one had a poor result and the remainder had excellent results.

CASE REPORT

(Operation performed by Dr. Thomas Shallow, Jefferson Hospital, Philadelphia, Penna.)

History P. C., white female, age 50, seen by us November, 1937, with a complaint of pain of three months' duration localized to the interscapular region and characterized by exacerbations and remissions. A productive morning cough, at times blood tinged, had been present for twenty years. Food regurgitation occurred occasionally. There had been progressive weakness, a weight loss of 18 pounds, and vague difficulty in swallowing. She was a fairly well preserved elderly woman of good color when first seen. Percussion note was impaired over the lower right thorax posteriorly. Chronic bronchitis was suspected.

X-ray A flat plate of the chest (Fig 1) revealed the heart shadow pulled over to the right side of the chest and a large dense sharply circumscribed shadow at the right upper lobe the size of a grapefruit. Following administration of barium by mouth a profound dilatation and tortuosity of the esophagus was disclosed (Fig 2). The mid-portion of the esophagus had the calibre of the cardiac portion of the stomach. The dilatation simulated a very large diverticulum in the proximal third of the intrathoracic esophagus. Esophageal lavage was instituted twice daily in preparation for direct visualization and an amazingly large quantity of retained foul-smelling undigested food was obtained before the washings returned clear.



Fig 2 Following administration of barium, tremendous dilatation and tortuosity of esophagus was revealed with large diverticulum due to achalasia (cardiospasm). Chronic esophagitis present.



Fig 3 Appearance of esophagus after 3½ year period of medical treatment with indifferent clinical response. Patient reduced to liquids. Marked weight loss.

Esophagoscopy The entire thoracic esophagus was enormously dilated. The walls were thrown in numerous folds suggesting diverticula. The mucosa was greatly thickened, the site of chronic esophagitis. Because of marked tortuosity, it was not possible to visualize the hiatus of the esophagus.

Medical Treatment Weekly esophageal lavages were continued for four months, tremendous amounts of food being obtained and the patient experienced considerable relief for the first time in years. Divulsion of the hiatus under the supervision of Dr. L. H. Cleif was begun in April, 1938, by means of an air-filled bag passed over a No. 2 buttonhole twist silk thread, thirty feet of which was first swallowed for firm anchorage. This was repeated at intervals for the next two years with symptomatic relief in the early stages but with less success as time went on. Repeated esophagoscopy studies and treatment convinced us that the patient's interests would best be served by a plan of surgical treatment since remarkably little was gained by all conservative efforts to secure improvement. In May, 1941, when even liquids were swallowed with great difficulty, she consented to surgical intervention.

Surgical Treatment Cyclopropane anesthesia by the intratracheal method was administered. The transabdominal approach was employed. Through a paramedian incision, the periesophageal tissue was loosened, the esophagus was freed by traction and drawn down and sutured to the cardiac end of the stomach. A "U" incision was then carried from the esophagus and into the stomach and the spur thus formed was sutured together and invaginated into the

stomach lumen. The stoma was closed by suturing the stomach serosa to the esophageal wall. The reflected serosa and fascia covering the esophagus along with the adjacent peritoneum were sutured over the gastroesophageal anastomosis. Sulfanilamide powder was implanted over the site. (Fig. 5)

After ten days of post-operative care, the patient was on a soft diet and made a satisfactory recovery. In X-rays taken post-operatively the opaque medium passed to the upper locule of a sharply demarcated biloculated shadow in the middle two-thirds of the right hemi-thorax and slowly filtered into the lower locule. Progress into the stomach through the anastomosis was markedly retarded, only a minimal amount passing into the stomach. At six hours there was a 90% retention in the esophagus. (Fig. 4)

To determine the efficiency of the functioning stoma, a tube was passed into the esophagus and barium administered through the tube under fluoroscopic control. Under these conditions it was possible to visualize only a small trickle of barium entering the stomach.

To date (Nov., 1942) her clinical course has been uneventful. There has been no food regurgitation or dysphagia. The back pain has lessened, appetite and strength have increased and she has gained 18 pounds. During this period she has had esophageal lavages to prevent food accumulation.

COMMENT

A significant finding deduced from the post-operative roentgenograms is the fact that little decrease in



Fig 4 Appearance of esophagus 4 months following esophagogastrostomy. Little change noted despite marked clinical improvement. Progress of barium into stomach through the anastomosis markedly retarded.

the size of the esophagus and an apparently poorly functioning stoma is seen in the face of an unquestioned marked relief of symptoms. This lack of correspondence between the clinical and X-ray findings has been commented upon by other observers, and has found corroboration in our experience with this case. Therefore, roentgenographic criteria should not neces-

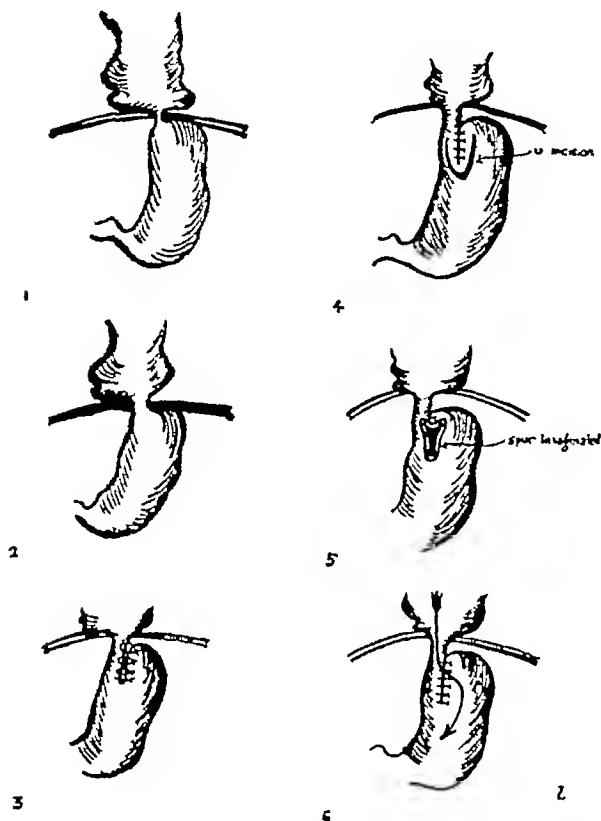


Fig 5 Schematic representation of stages of operation (esophagogastrostomy) performed for relief of long-standing achalasia consisting essentially of a short-circuiting of the cardioesophageal junction

sarily be employed solely in forming conclusions as to successful treatment.

It should be borne in mind that the course of development in this case as regards the clinical course, the pathologic changes, and the therapy necessary is far from being that of the typical case of cardiospasm. The presence of only a moderate dysphagia, relatively little pain and repeated food regurgitation in this history is not the usual anamnesis obtained, the discovery of a large saccular outpouching amounting to a

well-defined diverticulum formation is an associated lesion not commonly encountered in cardiospasm. Here it occurred in all probability as a direct consequence of the long standing obstruction.

The presence of associated lesions in cardiospasm merits more detailed mention. Many observers have reported their presence in this disturbance. Pylorospasm (achalasia of the pylorus) has been described in association with cardiospasm. Etzel (5) reports a concomitant megaesophagus, megacolon, megaureter and other digestive and urinary tract changes in a study of a large series of cases. He quotes Neto as stating that 68% of twenty-two cases observed disclosed megacolon. In the light of these facts, more complete search of the remainder of the gastro-intestinal tract and other systems (genito-urinary, cardiovascular) for other abnormalities would seem to be indicated in these cases.

When the triad of symptoms, substernal pain, dysphagia and regurgitation of food does not constitute the clinical picture, it is not infrequently confused with that of the pain of ulcer and with gall bladder colic. Many such patients have had abdominal operations for these conditions with fruitless results.

The differential diagnosis thus assumes justifiable importance in these cases. This rests upon the critical evaluation of the facts elicited in the history, roentgenograms and esophagoscopy. Upon the basis of early symptoms, it is difficult to differentiate cardiospasm from a malignant or benign lesion at the cardia, hiatus hernia or esophageal diverticulum. In the usual case, roentgenograms reveal a smooth obstruction at the cardia and a cone-like dilatation above. Under the fluoroscope, a fluid level of the barium is seen. The esophagoscope reveals superficial erosions, ulcerated areas, esophagitis and areas of varying degrees of thickened or thinned mucosa.

SUMMARY AND CONCLUSIONS

1 The successful use of esophagogastrostomy with consequent relief of symptoms is reported after conservative measures were ineffective in a case of long standing cardiospasm (achalasia) complicated by tortuous dilatation and diverticulum formation.

2 The degree of clinical improvement noted following operation was in contrast to the comparative lack of change in the appearance of the lesion as seen in post-operative roentgenograms.

3 Esophagogastrostomy appears to be the operation of choice when the surgical approach to the treatment of cardiospasm must be considered.

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Digestive Disturbances in Early Cardiac Failure

By

ANTON W OELGOETZ, M D
COLUMBUS OHIO

THE stomach is possibly more frequently subject to functional disturbance than any other organ in the body, and among the numberless causes which lie outside the digestive tract, one of the most important is heart failure. Cardiac failure is not always readily recognized in its earliest phases, nor is it sufficiently realized that digestive symptoms following circulatory congestion of the stomach and pancreas and liver may be among the earliest indications of heart weakness. Before the grosser signs of circulatory failure appear, such as edema of the extremities, and at a time when the accumulation of fluid may be shown only by a gradual increase in weight, there may appear a number of digestive symptoms which one might be prone to treat as primary gastro-intestinal problems, but which are due in reality to the fact that the heart, for whatever reason, is not doing its work efficiently.

If the true cause of the symptoms is recognized, they can be easily overcome by a period of bodily rest, either by prescribing a short vacation or asking the patient so to rearrange his daily work as to permit of short rest periods throughout the day. When this is done, the congestion of the gastric mucosa soon disappears, the normal secretion of digestive juices is again possible, and the mucosa of the bowel can again absorb gases, thus relieving the bloating and other symptoms present. Sometimes the use of digitalis causes nausea and anorexia, in which case it may be administered per rectum or parenterally.

In all such cases, where it is certain that the indigestion depends upon early cardiac embarrassment, it is well to begin treatment with a diuretic. Either the mercurial diuretics, such as salyrgan, or the xanthines, such as aminophyllin, bring about a more or less prompt and copious outpouring of the retained fluids, thus relieving the waterlogged condition of the organs and tissues, with early symptomatic relief.

While the diuretics are advisable in early cases and imperative in most advanced cases, they have the shortcoming of requiring repetition at intervals, and this repeated attempt to rid the body of bound water may cause weakness and exhaustion. Because the best diuretics have to be given intravenously and are therefore inconvenient for continued use, a simpler method was sought for controlling minor degrees of tissue congestion.

Strauss showed, in 1903, that sodium chloride is an important factor in water retention. Since that time it has become a routine measure to place cases of nephritis, hypertension, albuminuria and congestive heart failure on a so-called salt-free diet. But clinically the procedure has not been strikingly successful. It has not been successful because it has not been properly carried out.

The very term "salt-free" is incorrect. Life is impossible on a salt-free diet. The blood is a colloidal system. Salt, an electrolyte, is a necessary component of that system and its presence in definite quantity is absolutely necessary for keeping the blood cells in suspension and for maintaining the osmotic pressure of the blood stream. It is the salt in the blood and intercellular spaces which binds water. The quantity of water bound in the body is in direct proportion to the quantity of salt contained in the blood and intercellular spaces.

Patients with cardio-vascular disturbances have a reduced threshold for salt. As long as the salt intake is kept within this threshold, oedema and congestion do not develop. The purpose of this study was the development of a practical method for determining that quantity of salt which the cardio-renal patient can take without the development of oedema. Just as in diabetics, we determine the dosage of insulin which is necessary for the patient to metabolize sufficient carbohydrate to maintain weight and strength, so we determine the salt threshold for the sufferer from cardio-renal dysfunction. *The method here suggested enables the clinician to determine in terms of actual foodstuffs that quantity of salt which his patient can take with respiratory and digestive comfort.* When correctly carried out, no procedure in medicine is clinically more effective.

The limited salt intake has not been successful in many cases because the clinician usually contents himself by interdicting added salt, forgetting that foodstuffs themselves contain rather large quantities of sodium chloride. A full diet, without added salt, contains more than half the normal salt requirements of the body. Milk, for example, contains approximately two grams of salt per liter. Beef and other meats have a salt content of approximately 0.4 per cent. To be

clinically effective, *the daily salt intake must be one gram or less*, whereas the average diet, without added salt, contains more than twice as much

Unless one is familiar with the chemistry of colloids, it is difficult to understand how minute quantities of salt can be clinically so important. The blood is a balanced colloid. The cells are held in suspension in the serum by the electrical balance maintained by the negatively charged cells and the positively charged sodium ions. That is the reason *why blood must contain a definite quantity of salt*, why we cannot live on a salt-free diet. Too much salt likewise disturbs the colloidal balance. "Salting out" is a commonly used technique in chemistry for precipitating the particles in a colloid system from its liquid phase. Laboratory workers who work with syphilitic antigens (likewise a colloid) know how minute is the quantity of salt which will correctly sensitize an antigen. One hundredth of a cubic centimeter of a 10 per cent solution makes a striking difference. It would be interesting as well as instructive to know how many patients have been damaged by the administration of a too large quantity of normal saline solution following operation. A quart of normal saline contains twice as much salt as does a pint, and it is the *total quantity of salt injected that counts*, not the percentage solution. This point is far more important than is commonly realized.

In the accompanying table will be found most of the foods in common use, arranged in the order of their salt content. The foods are roughly divided into groups. These groups enable the housewife to make up her own daily menus from the articles available at the grocer. Milk, alone, makes up group one. Milk is relatively high in salt, but when taken alone the daily salt intake is easily kept below one gram. Milk is palatable without added salt and its actual low salt content permits the elimination of much salt from the body. The lists are further arbitrarily divided at points where occurs a rather large increase in the salt content, thereby giving us groups two and three.

In practice the limited salt regime is inaugurated with milk alone. This is continued for three days or until relief from indigestion and dyspnea follows. Foodstuffs from group two are then gradually added. The patient remains on foods from group two for one week. If symptoms do not recur, foodstuffs from group three are added, one by one, until a full diet is per-

mitted, with, however, the interdiction of added salt. If symptoms recur at any point, the patient is permanently placed on foodstuffs in the lower group. In this manner the patient's threshold for salt, in terms of foodstuffs, is quickly determined.

TABLE I
*Foodstuffs arranged in the order of their salt content
(After McLester)**

Proteins		Fruits		Vegetables	
Pork	04	Raspberries	0	Squash	002
Bacon	04	Watermelon	0	Brussel sprouts	004
Milk	05			Parsnips	004
Buttermilk	06	Grapefruit	004	Asparagus	007
Eggs	1	Blackberries	007		
Fish	3	Lemon	008	Onions	01
Oysters	4	Grape juice	009	Egg plant	01
Beef	4			Cucumbers	01
Lamb	4	Plums	01	Cranberries	01
Veal	4	Pineapple	01	String beans	01
Cheese	6	Pears	01	Tomatoes	01
				Cabbage	02
				Lettuce	02
Starches					
Tapioca	0	Grapes	01		
Honey	001	Apples	01	Kohl rabbi	05
Maple syrup	02	Cherries	02	Turnips	05
Potato	02	Peaches	02	Cauliflower	06
Rice	02			Pumpkin	06
Buckwheat	02			Radishes	06
Sweet potato	03	Rhubarb	03	Butabaga	08
Corn meal	03	Apricots	03	Chard	08
Lentils	06	Bananas	03	Celery	08
Oatmeal	06	Gooseberries	03	Beets	09
Barley	07	Strawberries	05	Watercress	09
Soup beans	09	Cantaloupe	06	Dandelion	1
Hominy	1	Prunes	06	Carrots	1
White bread	3			Endive	1
Rye bread	9			Spinach	1

*McLester Nutrition and Diet in Health and Disease

If the salt threshold is found to be too low to permit an adequate food intake, the diet must be supplemented with added vitamins. If the salt threshold is so low that sufficient food for nutritional requirements cannot be taken, the patient is placed on a *full diet, without added salt*, with the introduction of a "milk day" once or twice each week, to bring the salt intake below the symptom level. On "milk days" nothing is permitted except milk and water. Because it is salt which fixes water within the body, water need not be curtailed. Water in any quantity does not cause or increase oedema, if the salt intake is sufficiently low. Restriction of water is therefore of no value. Tea and coffee are permitted. In cases which are more advanced it is occasionally necessary to give an ampule of salyrgen and aminophyllin.

When managed in this manner, many months, sometimes years of respiratory and digestive comfort can be given these patients, who otherwise early succumb to congestive heart failure with all its distressing symptoms.

Tannin Control of Ileostomy*

By

MAJOR MATTHEW PEELEN, M D

KALAMAZOO, MICHIGAN

and

FREDRICK F YONKMAN, M D

DETROIT MICHIGAN

ONE of the most obstinate conditions causing no end of consternation to the physician is that situation which is presented by the patient with a terminal ileostomy or cecostomy from which considerable quantities of fluid are undesirably lost because of the intestinal refractoriness to all commonly accepted forms of treatment. The patient reported here caused considerable concern until she was eventually treated with acetyltannate and albumin tannate. Results were so unusually gratifying that we considered a report of the details was warranted, with the hope that similar patients might receive the same benefit as that experienced in our case.

Mrs. A. D., age 37, when first seen by a physician in New Mexico, presented the usual picture of ulcerative colitis which dated from December, 1939. There was marked diarrhea with bloody stools as frequent as twenty per day resulting in marked fatigue and loss of weight. Despite increasing severity of symptoms suggested treatment with neoprontosil was refused. Nine months later, following transfer of the patient to Michigan, the patient had gradually lapsed into a semi-stuporous state when she was seen in consultation with Dr. Martin Patmo. Neoprontosil, high dosage of combined Vitamins (A, B complex, C and D) and multiple transfusions improved her condition sufficiently to warrant her being up and about. X-ray studies of the colon revealed a well-advanced ulcerative colitis of the ileocecal valve and entire colon. Ileostomy was advised but refused and the patient was discharged with instructions regarding diet and care of the intestine.

Hospitalization six weeks later was necessitated by return of diarrhea, exhaustion and stupor. Medical treatment consisting of neoprontosil, vitamins and transfusions was again instituted but without improvement. X-ray examination revealed no change in colon pathology. Ileostomy was advised and performed. After a stormy post-operative session the patient gradually improved over a period of seven weeks and was discharged in fairly good condition.

One week later, because of her stuporous condition resulting from a "profuse flow" from the ileostomy which had continued for five days the patient was admitted to the hospital (Borgess) and given a slow infusion of 5000 cc of 0.85% NaCl and 5% glucose.

This treatment restored the patient to consciousness within five hours. All findings were typical of a dehydration toxemia, blood chlorides reached 352 and N P N 62. The patient was markedly emaciated, weighing 92 lbs. In an attempt to control the profound fluid loss from the ileostomy the patient was given bismuth subnitrate, 3 grams (grains XXXV) every four hours, and beginning two hours after the first dose of bismuth, she also received Tincture of deodorized opium, 0.010 gram (grains 1/6) every four hours, thus receiving alternating medication at two hour intervals. This did not control the flow from the ileostomy and stupor recurred unless 3000 to 4000 cc of physiologic saline solution were given intravenously at appropriate intervals.

Food by mouth increased fluid loss at the ileostomy as one would anticipate but abstaining from oral feedings, although diminishing fluid loss, did not prevent it. Attempts to improve the patient's general nutrition by oral feedings were continued for two weeks after which, despite her extremely poor condition, a colectomy in several stages was considered in order to obtain better control of the ileostomy. Dr. Frank Lahey and others have demonstrated the value of this procedure by invoking one of nature's laws of conservation, namely, that in the absence of the colon the terminal ileum usually assumes the functional capacities of the colon.

However, it occurred to us that the slow-acting tannin preparations might be of some value in this condition. Hence, Acetyl Tannic Acid, USP XI and Albumin Tannate, USP XI were used interchangeably. Fifteen grains (gr XV) were administered orally every four hours and the bismuth and opium regimen was discontinued. After 48 hours the number of stools had decreased from 20 or more to 8 and several were slightly formed. After 72 hours all stools were of somewhat firmer consistence and intravenous fluids were discontinued but food by mouth was allowed. Oral feedings were gradually increased in number and content with stool frequency maintaining at seven per 24 hour period. Within six weeks the patient had regained 12 lbs. of her weight loss, was considerably improved, able to walk and felt well enough to be discharged. She continued on acetyltannate or albumin tannate, gr XV four times a day and a routine ileostomy diet for the next two months. General improvement continued as well as gain in weight, which increased to 137 pounds three months

*From Borgess Hospital, Kalamazoo and from the Department of Pharmacology and Therapeutics, College of Medicine, Wayne University, Detroit.

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after the patient had been discharged from the hospital. This represented a weight gain of 45 pounds within 14 weeks after institution of tannate therapy. The patient continues in excellent condition but because of the condition of the colon colectomy is anticipated.

COMMENT AND SUMMARY

Severe fluid loss from an ileostomy refractory to oral bismuth and opium therapy was corrected by oral administration of U.S.P. XI preparations of acetil-tannate and albumin tannate. Sufficient fluid was conserved with these agents to allow discontinuance of intravenous saline and glucose infusion. The probable

mechanism of action of these tannin preparations is of interest. Benefit may have been obtained because of 1. Diminished peristalsis as prevails with these agents in the treatment of diarrhea, 2. Decrease in secretion of succus entericus, or 3. Promotion of more rapid absorption of ileac fluid. The latter seems most probable, not because of a specific effect on the absorptive cells per se but perhaps due to prolonged exposure of ileac fluid to absorbing mucosa, attending the lessened motility of the intestine. These tannin preparations might be of value in preparing the ileostomized or cecostomized patient for surgery as is indicated in this case.

Notes On Nutrition

The Canadian Nutrition Program consists of, (a) an advisory and educational effort concerning the adequate feeding of war workers, (b) advice and assistance to the public directly and through provincial and local nutrition committees, together with coordination of such educational work by private and volunteer agencies, and (c) other advisory and research activities in nutrition. War Industries are inspected and the provision of cafeterias or canteens, as well as good quality of food, can be legally required under penalty. At present 80 communities in Canada have active nutrition programs and the number is rapidly increasing. The research division is undertaking the compilation of food analyses as well as surveys of the dietary status of various social groups.

Corneal Vascularization as a Sign of Ariboflavinosis The corneal invasion by capillary growth may result from a lack of riboflavin and in such cases other obvious signs of avitaminosis will be found and the administration of riboflavin will bring about improvement. However, capillary invasion of the cornea may be the result of measles, with an accompanying conjunctivitis, and in such cases there will be no general signs of vitamin lack and the administration of riboflavin causes no improvement. (Pub. Health Reports 55 157, 1940), (Ibid, 57 1821, 1942).

A Short Method of Dietary Analysis This is based on the use of representative mean values for the composition of various types of food. The mean values are derived from the nutritive values for the most commonly eaten foods, as judged by special study of typical dietaries in a given area, and are computed on "average size" servings. Vegetables are divided into six groups. The data for 30 different food groups are collected into a single table, so that the food values for the group, times the number of servings quickly indicates the amount of the various essential food factors. (J. Am. Dietet. Ass'n, 18 492, 1942).

Diet and Lactation Evidence at present indicates that dietary factors, possibly specific ones, are necessary for initiation and support of lactation and this

finding might come to be of great importance in its application to human beings. Hormones are not alone responsible for lactation. The lactation factors L1 and L2 may be identical with the two vitamins p-aminobenzoic acid and inositol (J. Nutrition, 22 488, 1941), (Nature, 150 318, 1942).

Food for Overseas Forces The problem of satisfying the dietary requirements of overseas forces has many ramifications involving such varied questions as food requirements for various types of troops, palatability, keeping quality, packaging, space required during transportation, facilities for mass production, and protection from contamination. These are the types of problems which the Quartermaster's Subsistence Research Laboratory has been studying with considerable success. This laboratory has the difficult assignment of finding ways and means of furnishing all necessary information regarding the above mentioned questions, in order that army rations may be palatable and nutritious under adverse conditions of shipment and storage.

Interesting phases relative to food requirements of overseas forces have been covered admirably by Wodleka (Ind. Eng. Chem., 35 12, (1943)). Where it is possible to do so, overseas troops are fed Field Ration A, which is composed of perishable and non-perishable foods purchased, in part, in the area in which the troops are stationed. Master menus are submitted to service commands by the Quartermaster General. Food purchases are based on these menus.

Where food supplies are restricted and perishable foods cannot be furnished from this country, the men are given Ration B which is composed of nonperishables such as sugar, flour, salt and canned or dehydrated meats, fruits and vegetables. These are the types of rations fed to garrison troops both here and overseas.

"Operational rations" are issued where field kitchens cannot be used. Ration C is the chief operational ration and consists of six cans of food. Three of these, one for each meal, are identical—containing hard

candy, special biscuits, sugar and soluble coffee. The other three cans, one for each meal, contain, respectively, meat and beans, meat and vegetable stew, and meat and vegetable hash. These can be eaten hot or cold. Wodicka states that while this ration is better than the old "iron rations" of World War I, it is now considered somewhat obsolescent.

Ration D is an emergency ration containing three 4 oz chocolate bars that will not soften at high temperatures. These are reinforced with thiamine. The so-called "combat ration" is known as Field Ration K. Designed for parachute troops, this ration is likely to replace Ration C for combat troops. Three moisture and gas resistant packages, one for each meal, make up the day's requirement. Each package contains two types of biscuits, canned meat or cheese, a confection, a beverage concentrate, chewing gum, and four cigarettes. Canned meat, beverage concentrate, and confections are different for each meal. Wodicka states that tests in the field have shown that this ration is well suited for maintaining fighting efficiency and morale.

Wodicka states that the four guiding principles which must be used in designing a satisfactory ration are palatability, nutritional value, stability, and "caloric density." The latter refers to the maximum calories that can be concentrated into packages of a given size, to conserve shipping space. Instead of referring to "calories per ounce," subsistence officers now talk in terms of "calories per cubic inch." There are other factors which require study, such as ease of preparation, presumptive production capacity, cost, and physiologic effect.

Wodicka terminates his paper with an appeal for cooperation from nutrition specialists and food technologists in assisting the Quartermaster's Subsistence Research Staff in finding new and attractive food products which will meet the rigid specifications enumerated. He states that satisfactory desserts and stable sources of Vitamin C are needed.

Another important phase of the overseas food problem is that of packaging. Nelson (Ind Eng Chem, 35 16 (1943)) describes the types of packages that are required to meet the needs of overseas forces. He points out that food containers must be able to withstand the rigors of arctic and tropical climates. Protection must be afforded against moisture vapor, gases, odor transfer, grease transfer, insects and rats. Nelson lists the various materials used in manufacturing food containers and gives reasons why certain types of materials must be specified for special types of foods. Conditions are specified for the use of such materials as tinned containers, bondarized plate, lacquered metal, fiber cans, enameled steel, and the various types of laminated paper containers.

An interesting description is given of the research that has been done to find satisfactory films of plasticizing agents, waxes, coatings, lacquers, and adhesives for the manufacture of moisture proof container materials that will be suitable for dehydrated foods. Excellent progress is reported although few

details are given. Most of these new products have come into being because of the lack of critical materials.

The efficiency of various types of containers in protecting foods from war gases is discussed by Katz of Edgewood Arsenal (Ind Eng Chem, 35 20 (1943)). He points out that chemical warfare agents in liquid or finely divided solid form are likely to be more harmful than those in the form of gases or vapors. Since decontamination is difficult, it is the objective of the army specialists to protect the food completely from contamination, by suitable wrappings and coverings.

While hermetically sealed containers of glass, metal, or glazed earthenware provide perfect protection, excellent results have been obtained with cellophane films, multiple wrappings of heavy, well sized paper, and certain types of waxed and coated papers. Glue and sodium silicate, properly applied will make corrugated paper cartons resistant to chemical warfare agents. Methods of salvaging contaminated foods are discussed. Emphasis is placed on the necessity of proper inspection by qualified medical and chemical warfare officers before decontaminated foods should be used.

It would appear that there is truth in the statement that the American soldier is the best fed soldier in the world. It is also a matter of pride to know that our military leaders are not satisfied with the excellent progress already made but are seeking cooperation from scientists and technologists, with the hope of furnishing our combat troops with rations which compare favorably in palatability and which may actually be of higher nutritional value than the diets to which they have been accustomed at home.

Biotin Metabolism in Man Biotin is manufactured by intestinal bacteria, and the source of biotin for the human body is chiefly the supply so manufactured, for the amount taken in as food has relatively little influence upon the amount excreted in the urine. The total excretion of biotin is six times as great as the amount received in the food. Most of the biotin may be fixed by adsorption by egg-white or avidin, but there is a yeast growth-promoting factor of biotin which cannot be so bound by avidin. The only way in which the body could suffer a biotin deficiency would be through some diastolic interference with the life of the colonic bacteria (Am J Med Sci, 204 856, 1942).

Dietary and Plasma Proteins In protein starvation the body draws on the reserve stores of protein and upon the plasma proteins for its metabolic needs. A dog rendered hypoproteinemic by plasmaphoresis cannot build up its blood proteins unless the diet contains protein. The idea of the plasma being a possible source of protein in conditions where general protein lack is present, adds to the well-known functions of plasma from an immunological standpoint. All dietary proteins are not of equal value in building up plasma proteins. Among those which best serve this function are beef liver, beef serum, lactalbumin, casein, while

wheat gluten and gelatin are among the poorest Of medium value are fresh autoclaved yeast, bran flakes, rice polishings, polished rice, Irish potato, salmon, soy-bean and beef heart Of low potency are spleen, pork brain, beef stomach, canned salmon, pancreas and zein From this it appears that some vegetables are superior to certain animal proteins Further studies along this line are important because it meets the practical issue in protein starvation and possibly in recovery from anemia due to hemorrhage (Bull Johns Hopkins Hosp, 70 157, 1942)

Vitamin C and Infection The results of some feeding experiments in a large boys' school in England suggest that adequate intake of ascorbic acid has a real effect in helping to prevent sore throat, otitis media, pharyngitis, cervical adenitis, and possibly pneumonia and acute rheumatism (J Hygiene, Camb, 42 1, 1942)

Tissue Changes in Vitamin Deficiencies The pathology of vitamin deficiency embraces the immediate and specific primary effect on tissues and the secondary or general effects of the early changes on the body as a whole Four categories of effects can be noted (1) The effects of inanition, (2) Peripheral nerve and spinal cord degeneration in thiamine, pyridoxine, riboflavin and nonspecific skin lesions, (3) The skin lesions of nicotinic acid, pyridoxine pantothenic acid and riboflavin deficiencies, the unique degenerations of Vitamin E deficiency and the peripheral nerve lesions of thiamine deficiency, (4) The effects of A, C and D deficiencies The changes in the fourth category are not primary degenerations, but alterations in cell differentiation (Vitamin A deficiency), changes in developmental sequences (Vitamin D deficiency) or a failure in the production of an important structural element (Vitamin C deficiency) Epithelial changes, as well as possible nerve changes, accompany Vitamin A deficiency, with a disproportion in growth rate between skeletal and nerve tissues, which may result in overcrowding of the cranial cavity and consequent damage to the central nervous system Vitamin C deficiency results in failure of the mesenchymal tissues, as seen in scurvy The elements of Vitamin B complex are generally needed by all tissues and lesions develop only in those tissues which fail to obtain their quota (Physiol Rev, 22 233, 1942)

Dental Caries in the Hamster In a series of experiments on the Syrian hamster, it was found that the coarseness of the cereal fed had more to do with the development of dental caries than the presence of carbohydrate, and there was an hereditary strain which favored the development of caries (Pub Health Reports, 57 1599, 1942)

Colostrum and Vitamin A Cow's colostrum contains ten times as much Vitamin A, three times as much Vitamin D and riboflavin and twice as much Vitamin C as normal cow's milk. The percentage of Vitamin A strangely is unaffected by the nature of the diet prior to parturition Two hundred million pounds of cow's

colostrum are discarded annually on American farms, and it is too bad that this cannot be used In Scotland and Sweden the cow's colostrum is used to prepare a pudding which is considered a delicacy (J Dairy Research, 13 1, 1942)

Diet and Congenital Malformations Maternal dietary deficiency may result in the development of fetal abnormalities The protective substance which prevents these changes is contained in a 95 per cent alcoholic extract of liver (J Nutrition, 23 321, 1942)

The Color of Canned Peas Canned peas are not green but olive drab This is due to the fact that chlorophyll is changed to pheophytin by the loss of magnesium in the usual canning process By the new Blair and Ayres process this is avoided by the use of alkali and some traces of magnesium Such specialty items have to bear a special label statement that traces of alkali have been added (Ind Eng Chem, 35 85, 1943)

Uncomplicated Thiamine Deficiency Although it has been thought that the nervous symptoms and signs of beri-beri were due to the absence of thiamine in the diet, there was no reason to suppose that a human being developing the disease had used a diet specifically omitting thiamine, and it would be theoretically possible for the neurological symptoms to be caused by deficiency in associated food factors From some recent experiments in which it is believed that a true deficiency only in thiamine was produced, there were no neurological manifestations at all, and the animals died of cardiac disease with or without premonitory cyanosis and dyspnea Such death could be prevented by the administration of crystalline thiamine This would suggest that beri-beri, so far as its neurological manifestations are concerned, may be due to lack of other dietary essentials, rather than thiamine (Bull Johns Hopkins Hosp, 71 141, 1942)

Special Dietary Foods and the Law Under authority of the Federal Food, Drug and Cosmetic Act, section 403 J, "a food shall be deemed to be misbranded if it purports to be or is represented for specific dietary uses, unless its label bears such information concerning its vitamin, mineral and other dietary properties, as the Federal Security Administrator determines to be, and by regulations prescribes as, necessary in order to fully inform purchasers as to its value for such uses" This applies to food for "reducing," to baby foods and foods claiming to be non-allergic containing, as well as foods which claim to supply definite food essentials in stated amounts The contents of special food elements must be expressed in the amount contained in an average serving as compared with the daily needs of the individual for the specific substance The special label requirements are fixed by law but they differ from the National Research Council's "Recommended Daily Allowances"

Iron and the Vitamin B Complex in Man Many physicians like to treat hypochromic anemias with iron

plus Vitamin B complex, yet there is no support from animal or clinical experiments to show that the Vitamin B complex facilitates recovery from anemia, even in cases where there is an obvious deficiency in this vitamin group. Reticulocyte responses occurred during the use of iron alone in patients who were both anemic and lacking in the vitamin complex, and there was no secondary response after the addition of B complex, nor were such patients seen to recover more rapidly from the anemia when treated by both iron and Vitamin B complex from the outset (J A M A, 121:245, 1943).

Thiamine Deficiency in man Well-controlled human experiments on a group of physicians, produced a thiamine deficiency over a period of 5 weeks and the main symptoms complained of were fatigue, loss of efficiency in work, forgetfulness, constipation, irritability, paresthesia, nausea, diarrhea and joint pains, though not all symptoms were present in any one case, nor were any of the subjects ill or incapacitated. The feeding of 36 gms of dried brewers yeast per day to each person at the termination of the experiment promptly did away with these symptoms. The pulse rates tended to be slow during the experiment although no change in metabolic measurements was noted. The rapidity with which symptoms were pro-

duced was striking, and the effects on the personality were of importance to psychiatrists who are interested in the war effort.

Synthesis of Vitamins in the Digestive Tract There is no longer any doubt that vitamins are elaborated by microorganisms in the intestines of mice and rats, and presumably all animals. Vitamins of the B group are best produced when the diet of the animal contains a carbohydrate which is not all absorbed before reaching the cecum, for it is in the cecum that most of the vitamins are made by bacteria. However, these vitamins so manufactured are available to the animal chiefly through coprophagia. It is also known that the depression of growth which occurs in rats who are fed 0.5 per cent of sulfaguanidine is due to the fact that this drug inhibits the bacterial synthesis of essential growth factors in the natural Vitamin B complex and this growth depression is avoided by the feeding of yeast or yeast extracts (J Nutrition, 24:427, 1942), (J Exp Med, 75:277, 1942), (Univ Texas Publ No 4237, 125, 1942).

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Clinical Excerpts

SYNTHETIC VERSUS NATURAL FOOD VITAMINS

In the November issue of the Scientific Monthly, Professor A J Carlson presents an article on "Food and Fitness." He makes a plea for the return to natural foods. He states, "Nutritional safety lies in omnivorousness, in consuming, so far as possible, foods in their natural states, and, in the case of fruits and vegetables, eating some of them raw." He points out that the whole wheat, rye or rice bread is one of the least expensive protective foods. He states further, "On the whole we can trust nature as to the genuine nutritive elements in the whole grain—yes, trust nature further than the chemist and his synthetic vitamins." Recently, Professor Drummond, the scientific advisor to the British Ministry of Food, voiced this reluctance to put the dietary safety of a nation on synthetic vitamins as a long-range policy. He thinks we must and should provide the essential vitamins in the natural foods.

Now that the synthetic vitamins have been used by so many people for so long a time, I frequently have patients who present themselves with the expression, "I have used these vitamin pills for a year or more and here I am still suffering from malnutrition." All that was necessary to restore them to a good state of

nutrition was to put them on a diet rich in natural foods. Realizing that many patients will not take sufficient of the whole wheat grains to supply sufficient Vitamin B complex, I have employed the brewers' yeast powder with notable success. Of course, we cannot throw out all the synthetic vitamins, for example, Vitamin K and Cevitanic acid are of great value. But in regard to the other vitamin tablets that are dished out so freely today, I feel that perhaps the tissue cell with its billions of years of experience has learned to select its food from the blood stream and it may look with suspicion on the synthetic pills. With all of our advancement in science, that little cell is far superior to us in the judgment of its food requirements. For example:

For Vitamin A—The leafy vegetables such as kale, lettuce, etc., all yellow vegetables such as carrots, sweet potatoes baked with the skins on, etc., bananas, apricots, cantaloupe, cherries.

For Vitamin B—Whole wheat cereals, fruits, nuts, etc.

For Vitamin C—Citrus fruits, tomato juice, parsley, watercress, etc.

For Vitamin D—Egg yolk, butter, clams, oysters, salmon, sardines, etc.

H W Soper, Saint Louis, Missouri

Editorials

THE GLYCOSURIA CONTROVERSY

DR EDWARD TOLSTOI of New York City presents in this issue some of his own experiences gained from treating diabetics on the principle of permitting certain cases to show glycosuria during treatment. A perusal of Tolstoi's many contributions on this subject leaves the impression that his ideas are sound. He admits, for example, that if time and prolonged observation over many years should indicate that the practice of permitting a glycosuria is responsible for any deleterious effects on the patients, he would be willing to revise his opinions. Thus far, he has not been able to detect any adverse results from the practice, and he finds that in most cases of severe or fairly severe diabetes, the presence of glycosuria is a safeguard to the patient, and an insurance against insulin reactions, while in a few cases, whose reactions to insulin are uncertain, such a practice seems to afford the only reasonable method of insulin dosage.

From the time that Banting discovered insulin and it was placed at the disposal of the profession, it has been a not uncommon practice for physicians to permit some sugar to escape in the urine, merely because it was felt that this protected the sufferer from dangerous insulin reactions. Probably most doctors who did this had a slightly guilty feeling that they were transgressing a well-recognized "rule," because they had been indoctrinated with the idea that diet and insulin must be made to balance in such a way as to leave a glucose-free urine. As Tolstoi has frequently pointed out, there has not been any evidence accumulated to prove, in a scientific way, that a little leak of sugar does any harm to the body when protamine insulin is used. Many doctors will support the fact that some severe diabetics who refuse insulin altogether and who continually show glucose in the urine, get along remarkably well and live much longer without coma than one would expect. Furthermore, in the early days of insulin, it was common to see diabetics with damaged myocardiums die soon after being placed on a strict diet, high insulin dosage and with sugar-free urines. The writer had the privilege of working with Banting in the early days of insulin, and remembers how quickly Banting reacted to these instances and suggested to physicians, as well as patients whom he occasionally saw, to increase their carbohydrate intake, on the principle that "sugar is not poison."

In one sense, therefore, Tolstoi has merely given a scientific basis for what was already the instinctive judgment of many of the profession. Certainly, this work of Dr. Tolstoi's has stirred up a hornet's nest of opposition and unscientific protest. It has developed

into one of the warmest fights in the history of diabetes.

Our minds should remain open to both sides of the argument. The other extreme may be said to find expression in those authorities who even advocate "treating the blood sugar," i.e., using small dosage of insulin in cases who, though showing no glycosuria, continue to show elevation of the blood sugar levels. This practice seems at least a difficult one, especially in instances where one or more blood sugar estimations per day are suggested. In fact, we might ask ourselves if the diagnosis of diabetes is justifiable in cases which present only hyperglycemia. The Joslin group believe that Allen's work demonstrated that hyperglycemia is deleterious. Someone might also quote the work of Lukens and Dohan (*Endocrinology*, 30:175, 1942) which was done on cats. While valuable, this work strikes the writer as inconclusive, and it is not certain that animal work can safely be applied to humans. Only 19 out of 39 animals who had been subjected to partial pancreatectomy and received large doses of anterior pituitary extract developed diabetes, according to their standards. They also showed that in such animals, a high carbohydrate diet caused hydropic degeneration, whereas a low carbohydrate diet prevented such changes. Long, however, could not show similar lesions in rats made diabetic, even though they had high blood sugars from two weeks to several months. Banting made attempts to render dogs diabetic by partial removal of the pancreas followed by large injections of dextrose. I remember that some of these dogs, even after weeks of daily intravenous injections of very exorbitant amounts of dextrose, failed to become diabetic so long as there was a wisp of the pancreas left. We also know that a good many humans who are resistant to insulin and who have had hyperglycemia for years, show, at death, no lesion in the pancreas. If the opponents of Tolstoi can show that glycosuria actually does harm, or that a sugar-free urine actually does good, and can demonstrate these as scientific facts, then we believe that Tolstoi himself will admit the point. Thus far he has *scientifically* failed to detect any adverse effects of glycosuria on the patients. Thus far, he has *scientifically* found virtue in the practice of permitting glycosuria at times. He has the courage to state his findings and to fight back against what may be called a fixed idea which, on close examination, does not appear to have a scientific basis. Since we are all trying to practice scientific medicine, it will be necessary for each of us to examine the facts of the case and be guided by logic rather than by unsupported beliefs. In the case of protein metabolism, what is of importance is the amount of protein retained by the body, not the amount which is excreted. In the case of vitamin

Experimental Production of Gastric Ulcers in Dogs by Inducing Vascular Spasm with Pitressin*

By

A. J. NEDZEL, M.D., M.S.T.
CHICAGO, ILLINOIS

SINCE the time of the first good description of gastric ulcer by Cruveilhier (quoted by Strumpell (1)), many opinions and suggestions have been expressed concerning its etiology, and up to the present day there is no agreement among investigators on this subject. Clinical, experimental and post-mortem observations on the pathogenesis of gastric or duodenal ulcers furnish many conflicting views. Clinically, the disease was so overshadowed by local symptoms that the general symptoms remained in the background and did not attract much attention of physicians, and the underlying causes were overlooked. Experimentally, many ingenious ways of producing gastric ulcers were devised, and each method seemed to furnish an explanation of the mechanism of ulcer formation. On the basis of post-mortem observations, as early as 1853 Virchow proposed the theory that ulcers are caused primarily by nutritional disorders of the vessels, resulting from thrombi and emboli, which by interfering with the circulation lead to hemorrhagic infarct and to necrosis.

Though dominant for a time, Virchow's view did not explain many clinical observations on human material, and it lost favor when the period of morphological pathology came to an end and the trend in medical science turned toward functional pathology (Krehl (2)). Von Bergmann (4) founded a spasmogenic theory of ulcer development. According to it the disturbances in the vegetative nervous system are the factors that in many cases cause the spastic vascular contraction, be it through the contraction of the vessels of the mucosa proper (as Beneke proposed), or through spasm of the gastric musculature (Talma, Van Yzeien, Lichtenbelt) by which the blood supply to the mucosa is impaired (see Winternitz (3)). Consequently circumscribed anemic regions are brought about which are attacked by the digestive fluids. Further, according to the views of von Bergmann (4), through the loss of peptic substance there

may be evoked new spasms that will interfere with the healing process. In this way the existence of the chronic ulcer and the hemorrhages of the mucous membrane, or erosions and necroses of the same, as in acute ulcers, can be understood. Rossle (see von Bergmann (4)), at the same time offered a conception of ulcer as a secondary disease, the result of a neuroreflex action. Stewart (5), believed that in the production of an injury in the stomach or duodenum, which later is to become an ulcer the most frequent mechanism appears to be a focus of necrosis from vascular obstruction or stasis, a condition which can be brought about by a spasm of the arteries or of the stomach itself. Huist (see Stewart (5)) stated that the vasomotor spasm alone can explain the undoubted influence of sudden change of temperature in the production of relapses of gastric and especially of duodenal ulcer, and the frequent association of a poor peripheral circulation with this lesion. It is also a well known fact that spasmodic contractions of the stomach usually do happen in the presence of a chronic ulcer. This, of course, may aggravate the existing lesion. Hurst, too, emphasizes the importance of hyperasthenic gastric diathesis in the etiology of duodenal ulcer.

Certain persons have an inborn variation from normal individuals, and manifest it in hypertonus of the stomach with active peristalsis and rapid evacuation, and also with hyperchlorhydria and hypersecretion. Huist uses the term "duodenal diathesis," and states that a duodenal ulcer can not develop in the absence of such "diathesis." Stewart (1923) on the other hand, holds that "the comparative fixity of the lesser curvature, and the greater degree of trauma and friction from stomach contents to which the 'Magenstrasse' is subjected may possibly explain, at least in part, why acute ulcers in that situation are more liable to become chronic than in other parts of the organ." But the selective location of ulcers in the lesser curvature and in the duodenal bulb is easier to understand since Reeves (6) reemphasized how the anatomic peculiarities of the lesser curvature of the stomach and of the duodenal bulb differ from other parts. He found that the circulation in the vessels of the sub-mucous arterial plexus of the lesser curvature tends to be slow in comparison with that in other parts of the stomach. The vessels are much smaller, their length is greater, and there are fewer anastomoses. He also found the arterial vessels in the submucosal plexus of the duodenal bulb to be smaller and fewer, and to

*From the Department of Pathology, Bacteriology and Public Health in the College of Medicine, University of Illinois. This article is reprinted by permission from the book—Vascular Spasm by A. J. Nedzel, M.D., M.S., The University of Illinois Press, Urbana, Illinois, pp. 151-1948. \$2.75 cloth bound, \$2.25 paper bound.

†Associate Professor of Pathology, College of Medicine, University of Illinois.

Editor's Note: This article forms only one part of a series of experiments related to the effects of pitressin induced vascular spasm in dogs. The author's book "Vascular Spasm" indicates that endocarditis and a disseminated sclerosis of the nervous tissue also can be produced by this method. The present article deals only with experimental production of gastric ulcers by this technique. Dr. Nedzel's general thesis is rather iconoclastic; nevertheless it is well supported by pathological findings and deserves careful consideration by all gastro-enterologists. The Journal is indebted to him and to the University of Illinois Press for permission to reprint this chapter, also for the use of the valuable copper engravings which were loaned.

anastomose less freely, than those in other parts of the duodenum. Such anatomic peculiarities will lead in certain conditions to nutritional changes in the region predisposed to ulcer formation. In connection with such anatomic difference, studies have been made dealing with alterations of the ganglions and nervous tissue of the mucosa and submucosa, which may have a direct bearing on functional disturbances of the vessels.

Palmer (7) considers the local cause of ulcer formation as a chemico-mechanical one, and the underlying cause, a constitutional one, namely, a disturbance of metabolism. He defines gastric ulcer as a constitutional disease with local manifestations. Westphal and Kuckuck (8) point out that patients with definite gastric ulcer are persons with hyperergic irritable stomach, and in the large majority typically are stigmatized vegetatively. They are of an asthenic habitus, possessing fine curling hair, slightly protruding eyeballs, with somewhat dilated pupils and a slight, though definite, enlargement of the thyroid. They have a vasomotor hyperirritability, as manifested by increased dermographism, and they incline to hyperhidrosis of hands and feet from secretory hyperirritability of the sweat glands. Simultaneous with gastric ulcer there often exists a spastic constipation, evidencing a non-coordination of increased movements of the large intestine. Hitzenberger in 1920 (see Pines (9)) and others pointed to the fact that a round ulcer is formed in persons with an abnormal spine. The most frequent anomalies of the lower thoracic and the lumbar portions of the spine are hypernormal and left-sided scoliosis. In cases of lordosis the ulcer is usually found in the pyloric part, and in the cases of left-sided scoliosis it is in the center of the small gastric curvature. Pines (9), noting the existence of three theories of the pathogenesis of gastro-duodenal ulcers (the gastritic, the mechanico-functional, and the neurospasmogenic), thinks that in the majority of cases the components of all three play a part with one predominating. He like Hitzenberger and others, calls attention to the mechanical factor such as the curvatures of the spine. These curvatures, in his opinion, exert pressure on certain parts of the stomach and thus cause the appearance of the ulcers. He contends that his and other clinical observations in this direction support the mechanico-functional theory of the pathogenesis of gastric ulcer. Due to permanent anatomical conditions, the pressure exerted is of long duration, and thus the course of the disorder is extremely slow and never results in a complete cure. According to Carlson and Rivers (10), the factor common to all peptic ulcers, is the fact that the lesions occur only in tissues bathed by the acid-pepsin gastric chyme. Normally, though there are wide variations in the concentration of the acid juice, the mucosa is able to protect itself against ulceration. Yet, if for any reason, the margin of safety is decreased, and the defensive mechanism of the tissues is lowered, then the ulceration may develop in the presence of the gastric juice, though this se-

cretion does not possess any unusual erosive tendencies. Peipers (11) emphasizes the fact that during chronic lead poisoning the colic and the spastic constipation are not the only reactions of the gastro-intestinal tract. There is also a spastic tendency of the upper portions of the digestive tract with involvement of the vascular system. He shows that lead poisoning may produce the conditions which lead to the development of gastric ulcer. Just (12) found the incidence of multiple ulcerations and multiplicity of pathologic states to be greater than is believed. His findings on clinical material suggest that the multiplicity of lesions is present in all cases of duodenal ulceration.

Jankelson and Rudy (13), point to the simultaneous occurrence of peptic ulcer and diabetes mellitus. In persistent digestive disturbances, particularly of hunger and pain, peptic ulcer should be suspected and carefully investigated. Bujovich (14), when making injections for local anesthesia in persons with gastric ulcers, noted that the needle always pierced the skin with difficulty on account of considerable resistance. In cutting the skin and adjacent aponeurosis in the epigastric region the knife would meet special induration of these tissues, and the layers of the aponeurosis, once cut, would separate in such a manner that difficulty was encountered in reuniting them by suture. It appeared to him that the disorders of the nervous and circulatory systems of the stomach affect the skin and the abdominal layers and interfere with their nutrition.

Abrumovitz and Zabusova (15) analyzed 2,000 cases of gastro-duodenal ulceration and emphasized the role of faulty nutrition in the etiology of the disease. The authors concluded that prolonged fasting intervals and irregular eating caused by certain occupations play an important part in the pathogenesis of gastro-intestinal ulcerations. Kobro (16) studied cases with chronic unspecific disorders of the digestive tract. Half of his cases were leptosomes, but in all cases extensive indications of a vegetative neurosis, apparently with a vagotonic predominance, were observed. He finds a close relationship among all digestive disorders and between them and vegetative neurosis, chronic dyspepsia, in his opinion, is a forerunner of gastric ulcer. Constipation, colitis, primary chronic appendicitis, different phases of chronic dyspepsia, gastritis, and peptic ulcers—all these he considers as different stages and anatomic localizations of the same pathologic condition. Smithies (17), points out that the lesions of gastric or duodenal ulcer arise spontaneously only in the human family, not in any other group of living creatures, and that the basic mechanism of their production evidently consists in disturbances of the normal arterial blood circulation in the gastro-intestinal wall. He also states that some mural lesions evidently occur as a consequence of arterial, arteriolar or capillary occlusion (sclerosis plugging by clot, rupture, prolonged spasm). Also mural lesions may result from venous stasis prolonged to a degree sufficient to stop blood flow, and likewise from a complete

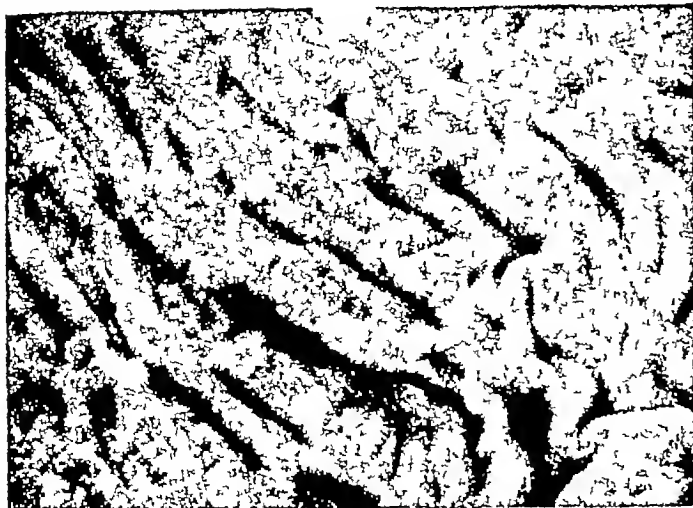


Fig 1 Gastric mucosa of dog 41 after injection of pitressin (About natural size)

lymph stasis. Bacterial deposits can be considered as "accidental," or secondary in the great majority of cases. Robinson (18) advances the psychogenic theory of peptic ulcer. He states that this disease is found only among the susceptible individuals of the white race, usually the long thin type who are given to worry and nervous instability. These individuals develop an unbalance of the vegetative system resulting in a bombardment of stimuli to the lesser curvature of the

stomach and duodenum, and in some cases producing vascular spasm, thrombosis, induration, ischemia, and finally necrosis and ulceration. Burger (19) points to the fact that the "Magenstrasse" suffers irritation more often and easier because of the passage of food, which may ultimately lead to vascular spasms in predisposed individuals.

Von Bergmann (4, 1934)) stresses the view that gastric ulcer is a manifestation of a systemic disease and should not be considered as a local disorder. Itching skin diseases frequently occur in patients suffering from stomach or intestinal ulcers. He suggests a similarity between some skin diseases and ulcer gastritis and thinks that by regarding the gastritis of ulcer as an "endematosis" some obscure factors in the pathogenesis of ulcer would be cleared up. Behneman (20) states that gastric and duodenal ulcers are manifestations of a systemic disease. He points to the long, thin, malnourished, underweight, poorly postured individuals who are subjects of this disease, and he remarks that there is also the element of an unstable nervous system in 95 per cent of peptic ulcer patients. Robinson (18) states that shock alone is sufficient to initiate an emotional upset leading to the spasm of the vessels and ultimately to ulceration, but that trauma *per se* can not produce a chronic ulcer, the ulcers following trauma heal rapidly and hydrochloric acid and pepsin do not deter the healing process. Hueck (21), analyzing the picture of gastric

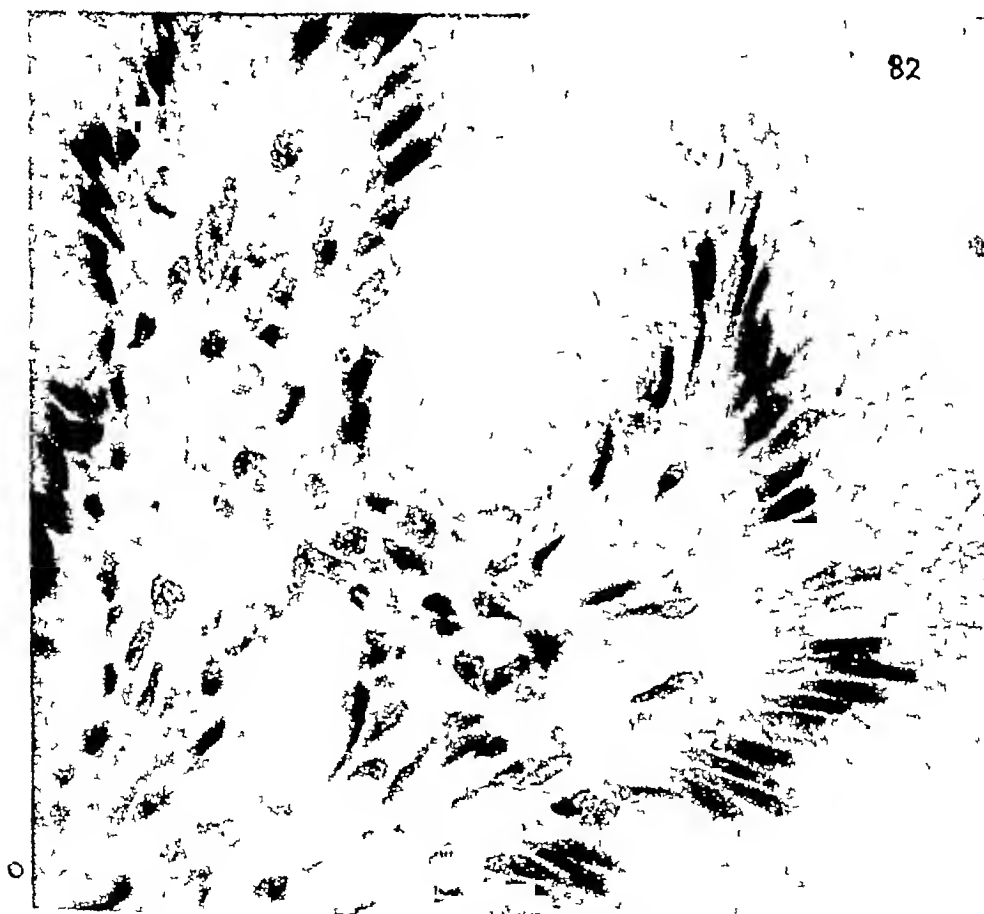


Fig 2 Gastric mucosa of dog 42 after injection of pitressin (X1100)

ulcer histologically, physiologically, and clinically, concludes that it is a result of an hyperergic state of the body which manifests itself in increased irritability of the vagus. Callahan and Ingham (22) conclude from their clinical observations that there seems to be a correlation between peptic ulcer and body build, personality, and other characteristics. Ask-Upmark (23), citing Cushing's opinion on the neurogenic origin of peptic ulcer, introduces his own clinical observations of cases with intracranial lesions in which a peptic ulcer developed. He also points to the other factors which participate in the pathogenesis of

peptic ulcer, and presents evidence to support the opinion that a definite relationship exists between the liver, carbohydrate metabolism, and the central nervous system. He considers these as a functional unit, disturbance of which may favor the development of such a lesion. That trauma and burns may cause gastric and duodenal ulcers is considered a well-established fact (J A M A 108 1452-2254). The association of pituitary tumors and gastric ulcers is shown in clinical material (Comroe (24)), Swan and Stephenson (25), thus suggesting the role of endo-

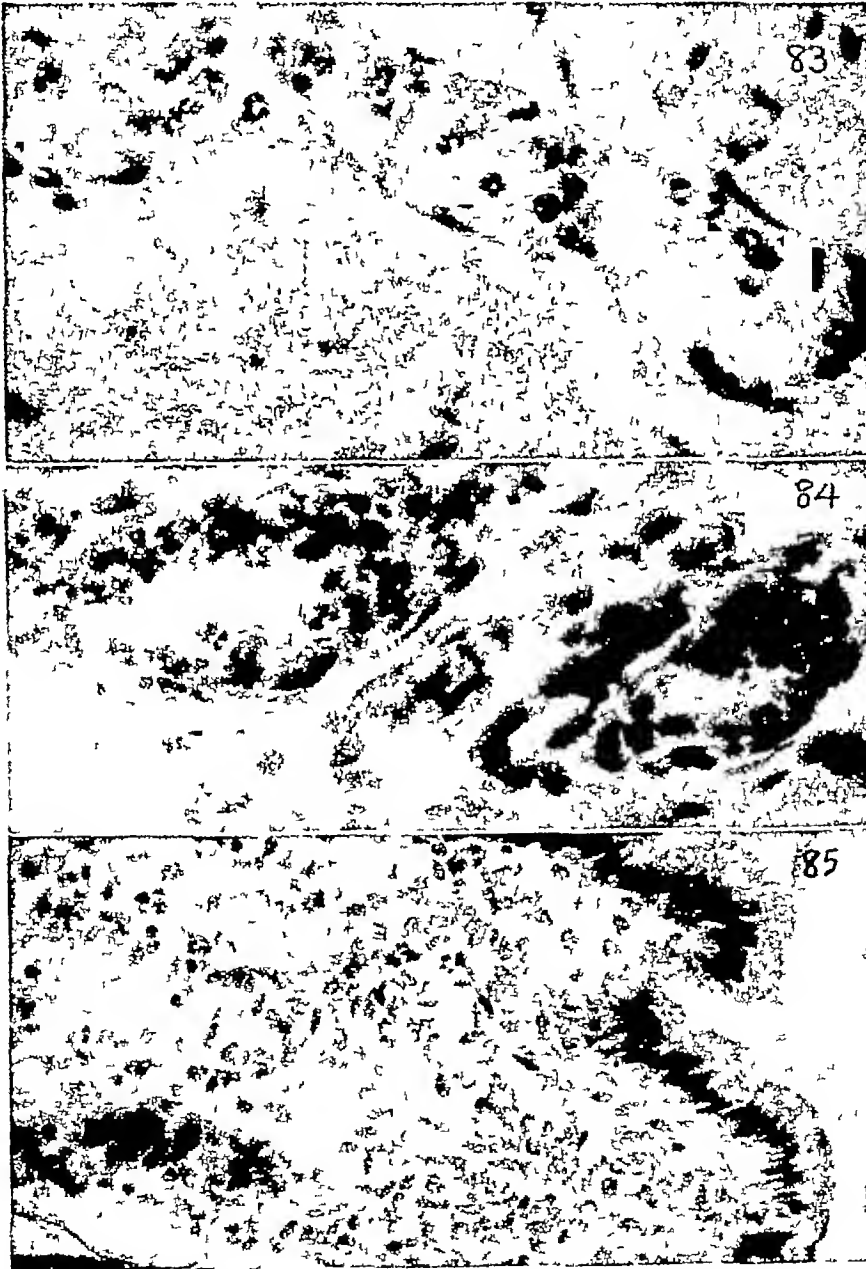


Fig 3 Dilated venule in gastric mucosa of dog 42 (X900)
Fig 4 Venule and arteriole in gastric muscle of dog 42 (X900)
Fig 5 Swelling of gastric mucosa of dog 43 (X300)

Practically all the many ingenious methods of producing peptic ulcers experimentally involve the integrity of the local blood supply, and lead in one way or another to nutritional changes in the walls of the stomach or the duodenum. A good review of these can be found in Rutimeyer's (26) paper. Some later methods may be reviewed here.

Shapiro and Ivy (27), using dogs and rabbits, established the anaphylactic nature of the local gastric reaction, like that of the cutaneous one (Arthur's phenomenon). These results were obtained by the employment of egg albumin, beef protein, oat protein, squash seed, globulin, edestin, hemoglobin and horse serum. Friedenwald, Feldman and Morrison (28) produced ulcers in most instances by the injection of a 1

per cent HCl solution into the gastric tissue. Injections of solutions of lesser strength gave inconstant results. The ulcers healed rapidly, but chronic ulcers could not be obtained by this method alone. Hanke (29) injected caffeine in cats with an empty stomach. At the end of two months, the stomachs of the animals showed chronic ulcers, which structurally resembled closely those of the human being. Possibly caffeine, he suggests, may play a role in the pathogenesis and development of peptic ulcers in man by causing an excessive outpouring of acid gastric juice on the mucous membrane of the empty stomach. Westphal and Kuckuck (8) point to the results of experiments on dogs which, under anesthesia, received faradic current on the vagus and injections of suparenin. Their his-

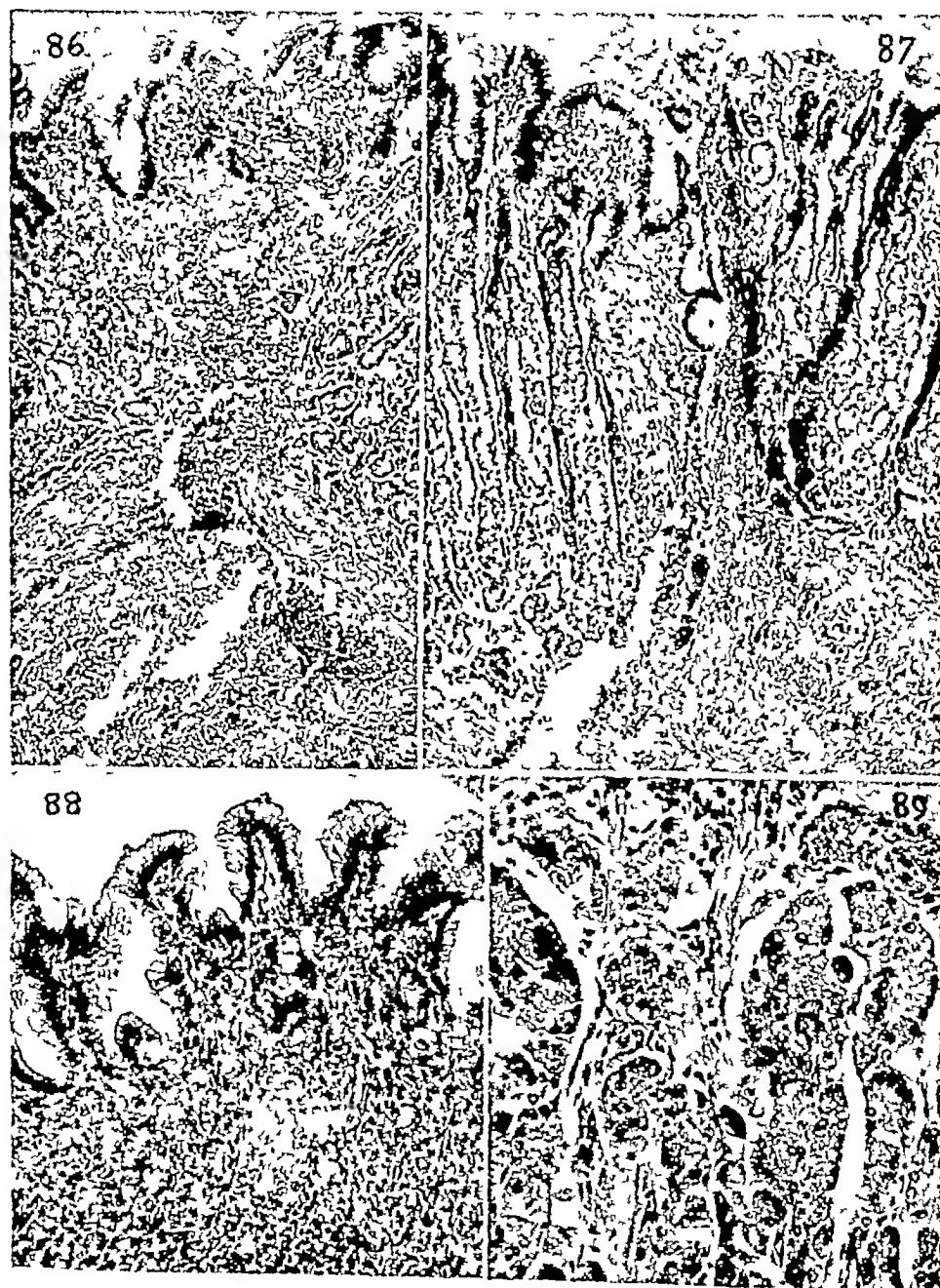


Fig 6 Gastric hemorrhage of dog 44 (X70)
Fig 7 Gastric hemorrhage of dog 45 (X70)
Fig 8 Gastric hemorrhage of dog 46 (X150)
Fig 9 Dilated blood vessels of dog 46 (X200)

tological pictures showed a great similarity to those of the resected gastric ulcers described by Konjetzny (30) who related ulcer formation to preexistent and coexistent duodenitis and gastritis, conditions which also are intimately connected with vascular activity.

It has been shown by Dodds and his co-workers (31, 32), and by Nedzel (33), that pathologic lesions may be produced in the gastro-intestinal tract of animals by injecting extracts of the posterior lobe of the pituitary gland. These lesions include multiple hemorrhages, erosions, and small and large ulcers of the stomach and duodenum, resembling those seen in man.

Windwer and Matzner (34) produced experimental gastric ulcers in rats by their pepsin-hydrochloric acid method. They also administered daily injections of histidine mono-hydrochloride (Larostidin of Hoffman-LaRoche), which did not prevent the formation of experimental gastric ulcers. A high incidence of lesions was recorded in the animals which received these injections. According to those authors, it is the conversion of histidine into histamine that is responsible for the production of experimental ulcer. Steinberg (35), found in dogs a relationship between the acidity, and jejunal spasm, and the development of the experimental ulcerations which closely resemble the duodenal and post-operative ulcerations in man. Steinberg did not deny the importance of the vegetative nervous system, the endocrine glands, or the constitution. He emphasized the equilibrium normally existing between the stomach and the duodenum, an equilibrium which can be disturbed in the individual with a certain constitutional predisposition and in an unfavorable environment. Balint (Vandorfy, 1936)

pointed to the fact that hydrogen-ion concentrations of blood and tissue in cases of gastric ulcer tend to the acid side, and that there are disturbances in the endocrine system. Vandorfy (36) also pointed out a change in the functional state of the stomach. In certain conditions Babkin (37) found the gastric secretion to deviate from its normal course. Conditions may arise which can produce destructive processes in the gastric mucosa. Histamine is present in the gastric juice after the subcutaneous injection of histamine, during sham feedings, or upon electrical stimulation of the vagus nerves, and its concentration changes with the change in rate of the gastric secretion. The histamine, acting upon the blood vessels, is capable of producing stasis in the capillaries, which may lead to the formation of erosions in the gastric mucosa. Babkin emphasized the possible role of histamine in the formation of peptic ulcer, thus evaluating some of the consequences of abnormal functioning of the gastric secretory mechanism. Bogoras (38) subjected his experimental dogs to a partial starvation, and succeeded in affecting multiple erosions and ulcers in five animals.

There is one thing in common in the clinical, pathological and experimental observations upon which the various views on the etiology and pathogenesis of gastric and duodenal ulcers are based, excluding direct trauma to the mucous membrane, whether it be physical or chemical, it is the normal function and the normal nutrition of the gastro-duodenal walls that prevents the ulceration. Any interference with or disarrangement of this function may lead to pathologic



Fig 10 Engorged vessels in gastric mucosa of dog 47 (X200)
Fig 11 Edematous tissue in gastric mucosa of dog 47 (X250)

changes in the corresponding regions and ultimately to ulcer formation. Normal function and normal nutrition of the gastro-duodenal walls, as of the other organs, depend directly on the behavior and the state of the blood vessels. It is this fact which led the writer to study the effect of pitressin on the gastric mucosa.

EXPERIMENTS

All the experiments were made on dogs (usually young) by administering a single injection, or repeated injections, of pitressin intravenously. The dose was 20 pressor units per five kilograms of body weight. The repeated injections were given at the average rate of two injections weekly until a total of fifty injections. The total number of dogs used was 62, of which 39 (63 per cent) gave negative, and 23 (37 per cent) positive results. The latter group showed lesions of the stomach and duodenum ranging from a small erosion to a large ulcer. A few of the dogs died from causes not related to gastric lesions, the majority were put to death.

It is advisable here to precede the detailed descrip-

tion of the histologic observations on the developmental course of gastric ulcer under experimental conditions with a delineation of the gastric mucosa of the living dog (under nembutal anesthesia) as seen by direct inspection after the animal was subjected to intravenous injection of pitressin.

DIRECT OBSERVATION

The stomach was exposed through an incision about 15 cm long in the median line of the upper abdominal wall. The organ was opened by an incision in its front wall, near the pylorus, and the gastric mucous membrane here exposed. The contents of the stomach, if any, were gently removed, and hemorrhage from the incision was stopped. The exterior of the stomach was constantly bathed with saline solution warmed to body temperature, and the injection of pitressin was made through the femoral vein. Attempts at direct photography failed because of the movements of the stomach after the injection of pitressin, and because of the respiratory movements of the diaphragm.

The degree of reaction varied in different dogs, but



Fig 12 Early necrosis in gastric mucosa of dog 48 (X250)

all reacted similarly. In a minute or more after the injection of pitressin the stomach contracted, and the folds of the mucosa became more pronounced and paler. A few minutes later the stomach dilated, the height of the folds was still increased, and red dots appeared on the surface without visible rupture of the mucosa. These dots enlarged, becoming from 1 to 3 mm in diameter. On careful swabbing with cotton pledgets, they disappeared transiently, only to reappear in the same or in adjacent places, definitely becoming visible hemorrhages. In about thirty to forty-five minutes, especially after two or three in-

jections of pitressin, the small hemorrhages definitely began to resemble small erosions and the mucosa became hyperemic with the folds disappearing (Fig 1, Dog 41).

HISTOLOGIC FINDINGS

At different stages of the observed changes, specimens of tissue were taken from the stomach, stained with hematoxylin and eosin, and studied histologically.

Fig 2 exhibits a bit of gastric mucosa near the surface, taken from dog 42, twenty-five minutes after an injection of pitressin. The capillaries beneath the

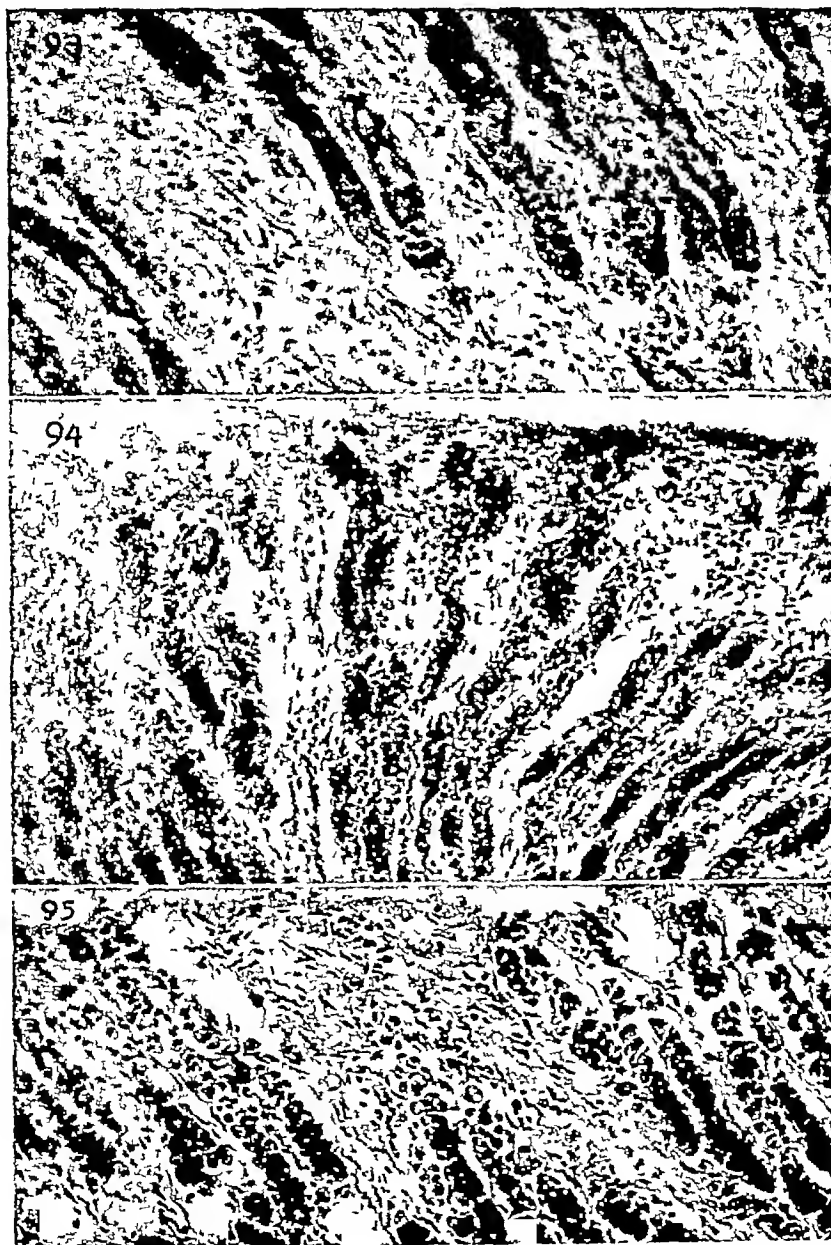


Fig 13 Edema and pyknosis in gastric mucosa of dog 49 (X250)

Fig 14 Lesion developing in gastric mucosa of dog 49 (X250)

Fig 15 Scar formation in gastric mucosa of dog 49 (X250)

epithelial layer are highly dilated and filled with the erythrocytes

Fig 3 shows another section taken from the same animal at the same time. The small vein is filled with leucocytes which are mostly polymorphonuclears. At the right, above the vein, is a small capillary with swollen endothelium.

Fig 4, taken from the same section as Fig 3 similarly illustrates the tissue of the muscular layer. To the left is a vein containing leucocytes, chiefly polymorphonuclears, accumulated at its walls, and to the right is an arteriole plugged with a thrombus, which consists of fibrin and red blood cells, while at the periphery are leucocytes, some of which are situated perivascularly.

Fig 5 depicts a section of mucous membrane at the surface, taken from dog 43, thirty minutes after an injection of pitressin. The mucosal surface displays an exudate. The epithelial cells are filled with some debris. The capillaries are highly dilated. The interstitial tissue is somewhat edematous. Round cells are scattered. The lymph channels are dilated.

Fig 6 reveals a small hemorrhage in the gastric mucosa, from dog 44, thirty minutes after the injection of pitressin. The blood vessels in the submucosa are widely dilated. One of them has been so overfilled that it has ruptured through the muscularis mucosae and the tunica propria to the surface, de-

stroying that muscular sheet in a small area and the overlying mucous layer in a larger area. The epithelial layer of the mucosa has also undergone destruction, permitting the escape of the blood on its surface. To the left of the hemorrhage a widely dilated capillary is seen. The surface of the mucosa is covered with fibrin.

Fig 7 presents a somewhat similar picture from dog 45. The blood perforated the mucosa, displacing the parts of this torn membrane, while relatively large amounts of blood are still seen at the base of the break.

Fig 8 shows a hemorrhage in the gastric mucosa of dog 46, taken thirty-five minutes after the injection of pitressin. The whole mucous layer of this stomach appeared shrunken. The blood vessels are contracted.

Fig 9, also from dog 46, displays highly distended blood vessels at the base of the mucosa. The glandular cells are beginning to lose their normal structure, and some of the nuclei are not visible.

The findings just described represent the initial stages in the development of gastric ulcer after injection of pitressin. Those presented in the following microphotographs are from animals put to death at varying time intervals after pressor episodes induced by injections of pitressin.

Fig 10 shows an effect of the action of pitressin in dog 47. This animal received intravenous injections

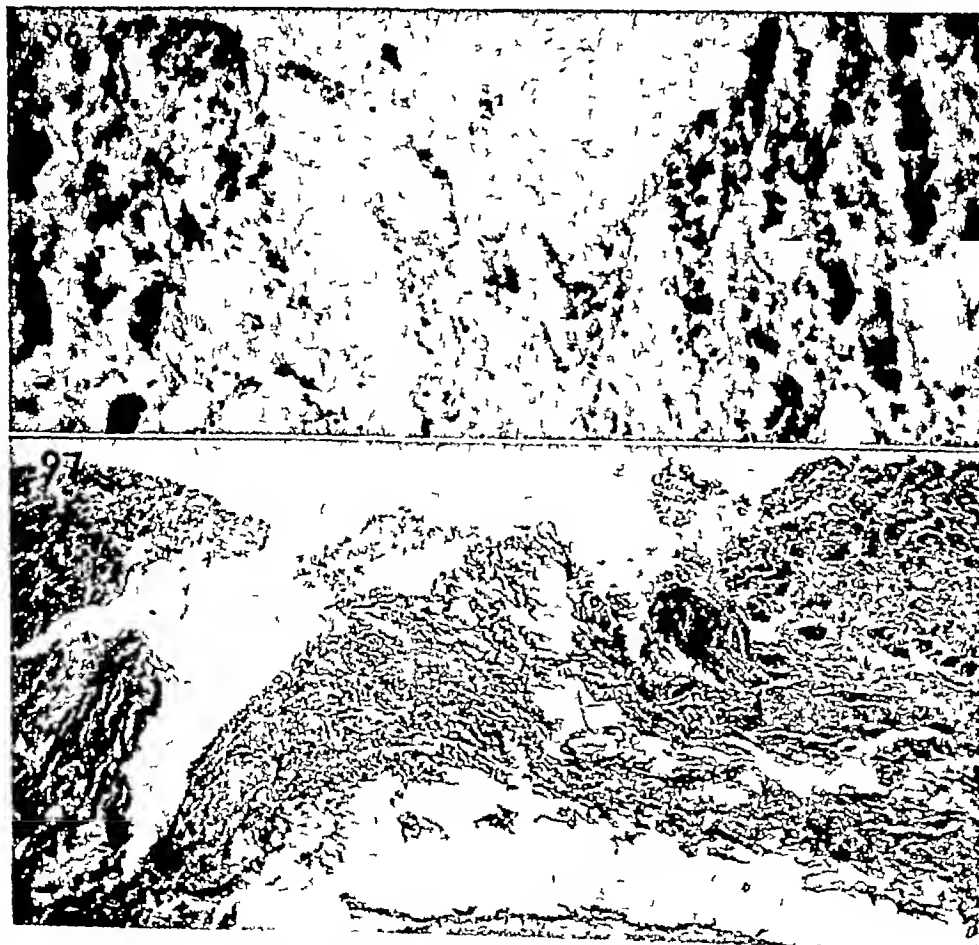


Fig 16 Superficial gastric ulcer of dog 50 (X200)
Fig 17 Gastric ulcer of dog 51 (X70)

on February 24 and March 3, 1937 and was sacrificed on March 9. Widely dilated blood vessels are observed in the mucosa of the superficial and middle portions of the specimen. Distended blood vessels are also found between the muscularis mucosae and the tunica propria. The nuclei of the gland cells and of the interstitial tissue are opaque, and the whole mucous membrane is edematous. The epithelial layer is comparatively well preserved.

Fig 11 portrays a part of the same section. The blood vessels of the submucosa are highly distended. The interstitial tissue is edematous. The blood vessel in the muscularis is filled with leucocytes, mostly polymorphonuclears.

Fig 12 illustrates early necrosis in a section of gastric mucosa from dog 48, which received an injection of pitressin on January 1, 1934, and was sacrificed twenty-four hours later. Only nuclear shadows, if any, of the glandular cells and tissue are seen. Below the faintly stained area is a row of scattered mononuclears. In a section from another part of the stomach of this dog there was a focus of disintegration in the central part of the mucosa, resembling a faint island in the otherwise normal-appearing stratum.

Fig 13 exhibits a lesion in dog 49, which received injections of pitressin on February 11, 18, 22 and 24,

and was put to death on March 2, 1937. Microscopically, the mucous membrane appeared swollen and reddened. Microscopically, it is edematous in toto, but mostly in its interstitial tissue. The nuclei of the glandular cells are deeply stained and some are not visible, while scattered mononuclears are present, and the glandular tissue appears somewhat shrunken.

Fig 14 is from the same specimen. The whole mucosal and submucosal structure is edematous, showing cyst-like accumulations of the serous exudate. The surface epithelium is absent, and the glandular tissue beneath the surface has partly disintegrated. The surface is covered with fibrinous exudate, most of which is invaded by connective tissue cells with formed elements. A superficial erosion is shown at the right. Mononuclear cells are scattered throughout the mucosa.

Fig 15 likewise is from the same specimen as Fig 13. To the other characteristic features is added an erosion which is filled with exudate and a proliferation of the fibrocytes.

Fig 16 represents a superficial erosion in the stomach of dog 50. Between March 3 and July 17, 1937, this animal received twenty-one injections of pitressin. It was put to death on July 21. The stomach contained a number of erosions and two small ulcers, one of which is figured here. The ulcer extends from

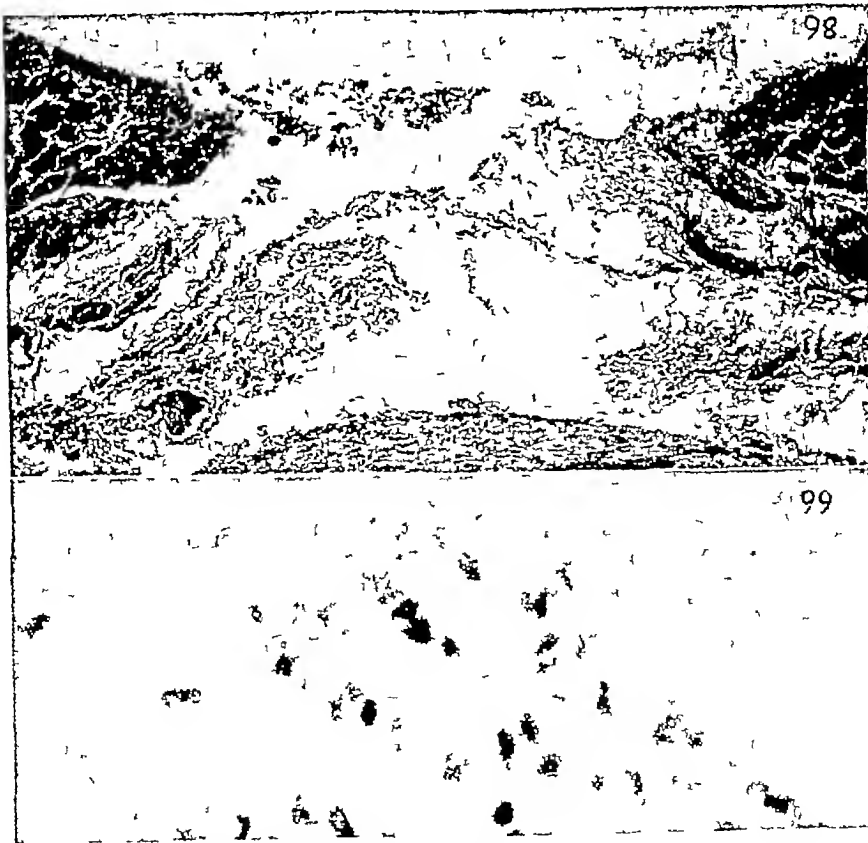


Fig 18 Gastric ulcer of dog 52. (X70)

Fig 19 Edge of gastric ulcer of dog 52 (X900)

the surface of the mucosa to the muscularis mucosae. There is some fibrinous exudate with moderate numbers of foamed elements. The edges of the ulcer are edematous with necrosis of the mucosal structure.

Fig 17 shows an ulcer from dog 51. This animal received thirty-five injections of pitressin between April 6 and July 25, 1934, and was put to death on July 25. A single gastric ulcer was found. It extends from the surface into the submucosa, perforating the muscularis mucosae. A serous exudate is seen in the submucosa. The edges of the ulcer show necrosis of

the mural structures. The muscular layer is edematous.

Fig 18 depicts an ulcer from dog 52. Between August 3 and 10, 1937, when the dog was put to death, it received twelve injections at the rate of two a day. The stomach showed several small ulcers. The one presented here penetrates deep into the submucous layer, its base formed by the muscular layer. In the lower right corner of the photograph, a partial involvement of the latter is seen. On the left, in the submucosal layer and just above the muscular layer,

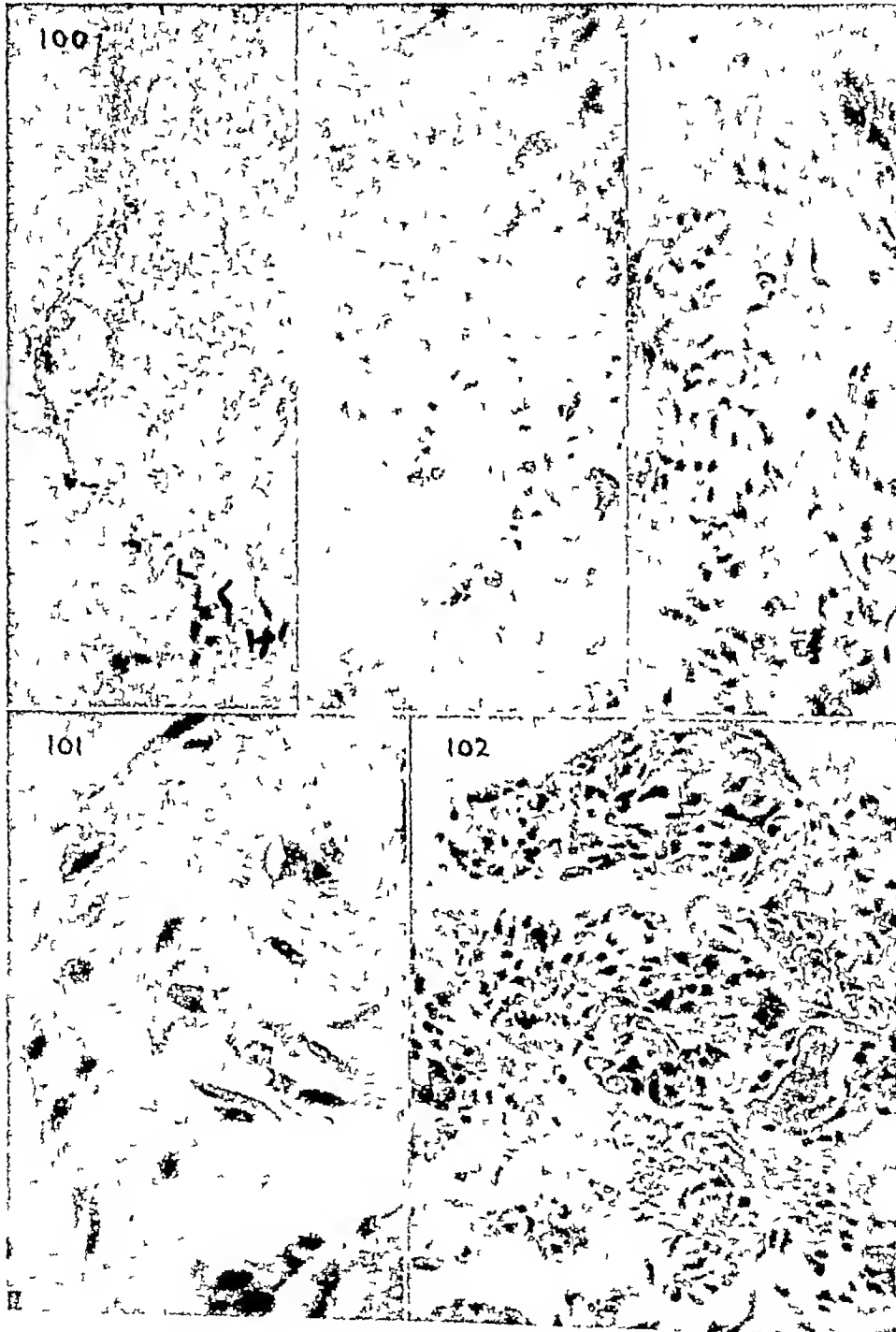


Fig 20 Gastric ulcer of dog 52 left, exudate, center, necrobiosis, right, healing (X250)

Fig 21 Healing of gastric ulcer of dog 52 (X800)

Fig 22 Healing of gastric ulcer of dog 52 (X500)

there is a blood vessel with a thrombus completely obstructing its opening. The ulcer contains some fibrinous exudate and debris of the mucosal and submucosal tissues.

Figs 19, 20, 21 and 22 are microphotographs taken under oil immersion of different parts of the edges of a gastric ulcer in dog 52. They display the different processes which are proceeding in the ulcer at the same time. Fig 19 shows a practically complete destruction of the glandular tissue, with a total absence of the endothelial layer. Fig 20 shows three different stages of the same ulcer found in the same section. Here the exudate has no formed elements, with the exception of bacilli, which are engulfed in it. Here also we get a picture of necrobiosis, in which some structures are completely destroyed, and a healing process in which fibrous cells penetrate through the exudate with the ultimate production of scar-like

results are presented graphically in Fig 24. Its upper part gives the total number of dogs (broken lines) and the number of dogs with positive findings (solid lines) by months, starting with September. As seen in the figure, the highest percentage of positive results, in relation to the number of dogs used falls in the months of December and January and again in March and April. In the lower part of Fig 24, where only the animals with positive findings appear, the results are expressed as percentages of the total number of dogs and are grouped by seasons. In the autumn months, September, October and November, 15 dogs were given injections of pitressin, and in 20 per cent the findings were positive; in the winter months, December, January and February, the 18 dogs treated gave 50 per cent positive results; in the spring months, March, April and May, 13 dogs yielded 61 per cent positive results, and in the summer months, June,

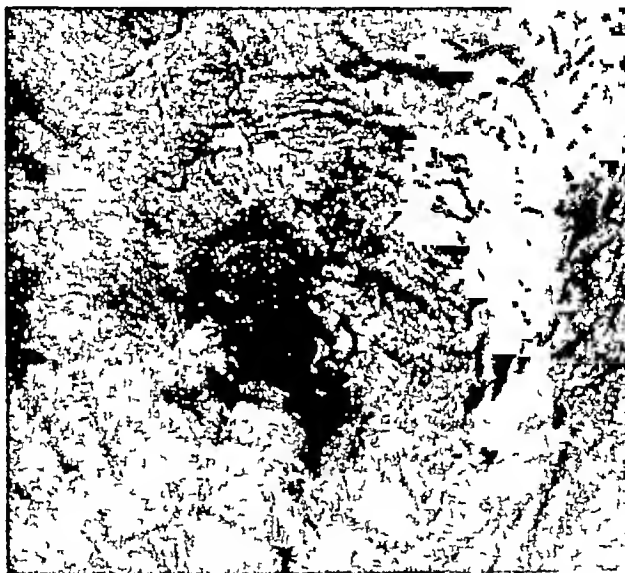


Fig 23 Pyloric ulcer of dog 53 (About natural size)

tissue. Fig 21 portrays the same healing process, but far more advanced. In the center is a newly formed capillary. Fig 22 depicts the healing process in glandular tissue. The cells appear fairly normal, though they are bathed in blood, and many capillaries are dilated and filled with erythrocytes.

Fig 23 shows a large ulcer in the pyloric part of the stomach of dog 53. Between March 22 and May 21, 1934, when the animal was found dead, it received fifty injections of pitressin.

All the experiments described were performed on healthy animals, the weak or sick were always discarded. The experiments continued during the entire year, and the number of animals used each month was approximately the same. This gave an opportunity to study the relationship between the positive and negative findings in the animals that were subjected to pitressin injections, and the month and season. The

July and August, there was a 23 per cent positive result in 16 dogs subjected to the experiments.

DISCUSSION

The observations already presented definitely point to a conditioning of the blood vessels as the immediate cause of ulcer formation, and indicate that the "spasm theory" is the most logical one to explain the periodicity in the appearance of ulcers, as well as the fact that acute ulcers are frequently multiple and tend to be irregularly distributed in the stomach and the duodenum.

Pitressin injected intravenously evokes spasm of the small blood vessels as well as spasm of the muscular tissues, which in their turn add to the compression of the blood vessels. The contraction is later followed by dilation of the same blood vessels—the act of restoration. A normal biologic rhythm of this type keeps the vascular supply and demand in constant equilibrium.

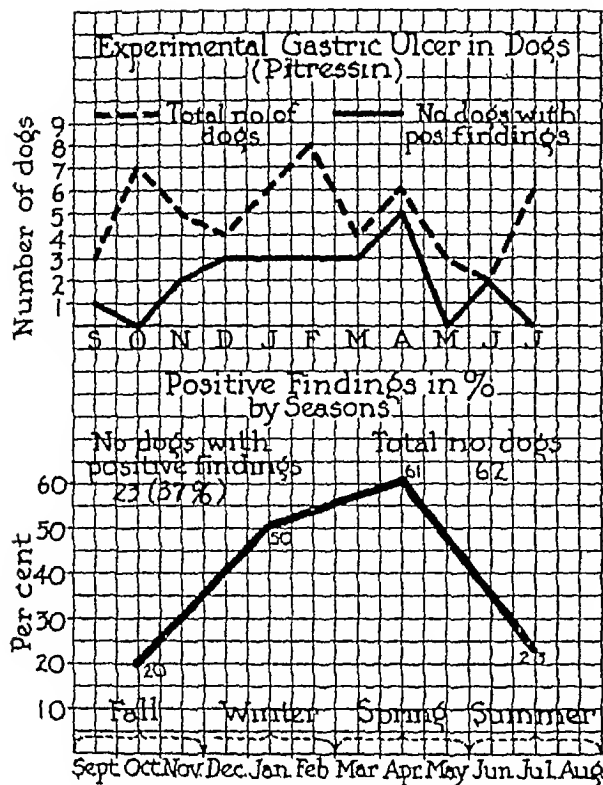


Fig 24 Graphic summary of experiments with 62 dogs

brum but the same contraction whether due to changes in the blood vessels or to contraction of the extrinsic muscles will, if prolonged or exaggerated, injure the parenchymal cells, because it will be associated with undue general or local anoxia

The greater the discrepancy between the demand for oxygen and the supply, the greater are the changes which will follow, the range extending from purely functional changes, which can not be discerned histologically, will lead to necrosis of varying extent in different stages. This is shown in detail in the present monograph, not only in the production of experimental endocarditis and gastric ulcer, but also in the production of analogous lesions in brain, liver and kidneys, as described in subsequent chapters. With the pressor phase as it occurs under natural conditions of life (i.e., with cold, with relative alkalosis, with sympathicotonia, etc.) or after injections of pitressin, contractions of the blood vessels occur which may reach such a degree that a vessel filled with blood may rupture and establish a hemorrhage directly into the lumen of the stomach (Figs 7 and 8). In its mucosa

small hemorrhages and also foci of necrosis can be observed, and in the submucosal and muscular layers dilated blood vessels filled with leucocytes, some of which are perivascular in position, are visible. On the surface of the mucosa an exudate may collect, containing fibrin and formed elements which have passed through the undamaged epithelial layer. Erosions, edema of the wall of the stomach, necrosis of the mucosa, associated with an increased number of mononuclear cells, healing of the erosions, and ultimately, typical ulcer formation may also be discerned.

The ulcers of the stomach produced experimentally, as well as those established clinically, heal readily. The so-called chronic ulcers, of the type shown in Fig 23 require an additional factor, also of nutritional character, and do not occur so commonly.

The regularity with which peptic ulcers are found in certain persons leads some authors to speak of an ulcer diathesis, thus associating ulcers with definite constitutional trends in persons subject to this disease. It is generally agreed that ulcers are the result of metabolic disturbances, the local cause being chemico-mechanical and the underlying one constitutional. Since the constitutional picture is quite overshadowed by the urgency of the local symptoms, the latter have led, and still do lead, to the almost exclusive consideration of the ulcer rather than of the patient as a whole. But it is well recognized that persons subject to ulcer formation are usually slender (asthenic persons) with labile nervous and vascular systems. The disease is seasonal and occurs mostly in the northern latitudes, and Peterson (39) showed that the exacerbations are connected with certain meteorologic changes.

The seasonal character of the disease can be related to the observations reported here. It is likely that the seasonal variations are in part connected with the systemic stimulation of the entire organism during the late winter and spring, at least, there is then a greater tendency toward inflammatory reaction and toward digestion of tissue.

It seems that normal animals which have been fatigued and are more acid, and thus biologically weaker, reveal greater autonomic difficulty in adjustment to meteorologic changes, and in them superimposed pressor effects from injections of pitressin apparently lead more readily to prolonged spasm and to delayed recovery from the effect of spasm.

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Low Incidence of Cancer of the Stomach in Iowa

By

F. W. MULSOW, M.D., Ph.D.
CEDAR RAPIDS, IOWA

THE title of this presentation may seem somewhat facetious, since most textbooks and authors discussing cancer of the stomach stress its frequency. So few cases of cancer of the stomach had been seen over a period of years that a study of the local incidence and diagnosis of gastric cancer was begun in 1935. This study has continued and has extended to include data, from the Tumor Clinic of the State University Hospital at Iowa City, and from the Iowa State Department of Health, at Des Moines. From this study it appears that many textbooks and writers in medical journals have over-estimated the frequency of gastric cancer or that cancer of the stomach is not as frequent in Iowa as it appears to be in other parts of the United States.

In Osler (1) the following statement is made: "In an analysis of 30,000 cases of cancer, W. H. Helch found the stomach involved in 21.4 per cent, this organ standing next to the uterus in order of frequency." This same statement appears in the third edition of Osler (1898), which suggests that there has been little change during the past 40 years or more, in the incidence of cancer of the stomach. Cecil's (2) Text Book of Medicine says: "It is estimated that gastric cancer constitutes one-fourth to one-third of all deaths from cancer." It is stated in Musser (3) that "Cancer of the stomach is responsible for a large percentage, perhaps 30 to 40 per cent of all cancer deaths." Ewing (4) says that Gurlt's statistics of Vienna of 10 per cent in 4131 cases of cancer are much too low for gastric cancer and that Haberland's figures for Switzerland of 41.5 per cent in 27,511 cases are much too high. Yet Ewing refers to others who report a much higher incidence. Among these is the data of Cramer, who found that of the total cancer mortality gastric cancer in England contributes 55.8 per cent in males and 42.3 per cent in females. The highest incidence referred to by Ewing has occurred in Norway about which he says: "In Nordlandet, Norway, where the diet is largely fish, Seagard finds a mortality from gastric cancer of 74 per cent of the total deaths from cancer."

Cutler and Buschke (5) says that "Carcinoma of the stomach comprises one-third of all malignant tumors." Walters, Gray and Priestley (6) say: "There is an often quoted statement to the effect that approximately 38,000 persons die annually in the U. S. from cancer of the stomach." They also say that its incidence is increasing. This same 38,000 figure is quoted by Christopher (7) in his surgical text book. In the Proceedings of the Staff Meetings (8) of the

Mayo Clinic is this statement: "Of this number (160,000 cancer deaths) about 50 per cent or 80,000 die from cancer of the gastro-intestinal tract, and of these 80,000, approximately 50,000 die of cancer of the stomach." These figures were taken from a report by Dublin, of the Metropolitan Life Insurance Company. Cramer (9) says: "In this country about 30 per cent of the total recorded mortality from cancer is represented by the recorded mortality from gastric cancer." Mullen (10) in discussing cancer of the stomach says that "It comprises 35 per cent of all cancer, causes one-third of all cancer deaths, and results in more than 100 fatalities every day." Many other quotations could be given from text books and journals, giving cancer of the stomach as the cause of 25 to 40 per cent of all cancer deaths, but it seems unnecessary to use more space for such quotations.

The study to determine the incidence and means of diagnosis of cancer of the stomach in Cedar Rapids was begun in 1935. All of the deaths reported at the City Hall were examined for the 5 preceding years, but the reliability of the diagnosis seemed so uncertain that the study has started from that date. All death certificates have been examined since then with special emphasis to cancer of the stomach and abdominal cavity. Further information regarding the methods of diagnosis was obtained by consulting with the physician who had signed the death certificate and examining hospital records in many cases. The physicians cooperated very well in this work.

During the past 8 years there have been in Cedar Rapids, 734 deaths from cancer and other malignant tumors. There were 91 deaths or 12 per cent, reported as being due to cancer of the stomach. In many instances the diagnosis was made on very little definite findings. It is well known that gastric cancer is difficult to diagnose and the diagnosis is often made at the necropsy and in a few cases with difficulty then. The methods by which the diagnosis was made is given in Table I. The most certain method is at the top of the table and those given below are given in order of their importance. Those listed under autopsy may have been explored or had X-ray studies, but those listed after X-ray did not have a biopsy or autopsy or exploration. In those made on clinical findings alone the diagnosis cannot be very accurate, since cancer of any part of the abdominal cavity may give such symptoms as nausea and vomiting with loss of appetite and weight. Many of those listed as doubtful are probably not cancer of the stomach, as was found by consulting with the attending physician and hospital records.

A few examples as to how the diagnoses were made may be of interest. During the year 1942, there were 10 cases reported as having died of gastric cancer. Of these cases one was confirmed by biopsy, two by biopsy, two were explored but no biopsy was made, and one was diagnosed by X-ray. One that was diagnosed on clinical findings was a woman 68 years old who had lost considerable weight and had persistent vomiting with blood frequently present. This woman may have had any one of a great many abdominal conditions. Three in the doubtful list consisted of a man 68 years old and a woman 80 years old. Both of these gave a long history of stomach trouble with a previous diagnosis of peptic ulcer 5 or more years before they died. In spite of this history and no laboratory findings the death certificate gave the cause of death as cancer of the stomach following chronic ulcer of the stomach in both cases. The third case listed in the doubtful class was a man 73 years old who died from bleeding of the gastrointestinal tract with the vomiting of bright red blood and tarry stools. In talking with the physician in this case he said that he probably made the diagnosis on the little evidence and after more study he probably had the death probably due to a bleeding peptic ulcer. Here in the year 1941 there were 5 deaths attributed to cancer of the stomach among 101 deaths from cancer of other malignant tumors. Three of the 5 had been explored and a biopsy taken in two. One diagnosed on clinical findings was a woman 61 years old who had many apparent metastatic tumor nodules of the skin and frequent vomiting of small amounts of red blood. In talking to the physician in this case he was not sure as to the nature of the skin tumors and did not consider ulcer as the cause of the stomach trouble in a patient of this age. One in the doubtful class was a man 69 years old who was ill about 7 months with his final illness. He had a long history of recurring stomach trouble. His last illness began after a heavy Thanksgiving dinner from which he did not recover, as he had in previous similar attacks and his condition again became worse after a New Year celebration. About a month later he was taken to the hospital where he died 10 days later of apparent pyloric obstruction. He had epigastric tenderness but no mass, he could retain very little food on his stomach. The Hb was 82 per cent the red cells 1,760,000 and the white count was 8,200. The urine was normal. The death certificate gave cancer of the stomach as the cause of death. All of those placed in the doubtful class had been diagnosed on very little positive evidence, but it would serve no purpose to describe all of these. Five were reported as cancer of the stomach when in reality after talking to the physician reporting the case, cancer of the abdominal cavity was meant. It is well known that the term "stomach" is often used to cover any condition of the abdomen, especially when there is vomiting. In many others the patient refused X-ray examinations or hospitalization or were seen only a few times by the

physician, who more or less guessed at the final diagnosis.

During the past five years a special study of all abdominal malignancies reported has been made. Of 151 cases reported as having died of rectal or colon cancer 159 or about 60 per cent are confirmed by X-ray exploration or biopsy examination. Of 52 cases of cancer of the liver, 140 facts on gall bladder 34 were explored and the stomach found free of cancer 8 others were found at autopsy, and 5 by X-ray studies were found to not have cancer of the stomach but the clinical evidence of disease of the liver. The remaining 6 cases had jaundice and other evidence of disease of the liver, but the origin of the disease is very uncertain from the history of the case.

In 21 cases of cancer of the pancreas, 21 were operated upon or examined at autopsy. 5 had pancreatic jaundice and other symptoms rather characteristic of pancreatic disease. 2 were diagnosed on rather good clinical history and findings.

The 16 reported as abdominal cancer were apparently for the most part cancer of the colon. But there were no X-ray studies and the diagnosis depended largely upon the presence of an abdominal mass or partial bowel obstruction. 4 of these were cancer. The frequency of the more common forms of cancer is shown in Table II.

In the Tumor Clinic of the State University of Iowa at Iowa City, the incidence of cancer of the stomach was 5.0 per cent during the past 5 years. Among 2,755 cases of cancer of other malignant growth there were 140 cases of cancer of the stomach. This low incidence may be due in part to the fact that many forms of cancer are cured at least temporarily and do not come to the hospital. Hence the rate is less than it would be in mortality figures. Also other forms of cancer such as cancer of the prostate, bladder and skin are much more frequent than in general mortality figure. And finally the diagnosis of cancer of the stomach was not made unless confirmed by X-ray studies, gastrotomy examinations, operation, or biopsy which has excluded many clinically diagnosed as cancer of the stomach. The frequency of common forms of cancer at the Tumor Clinic of the University Hospital are given in Table III. These patients come from all over the State and are composed of those who cannot receive proper treatment and diagnosis in their local community and should include a representative share of gastric cancer.

In a report of the Division of Vital Statistics for the State (11) of Iowa in 1941 it is shown that there were 3,660 deaths from cancer and other malignant tumors. Cancer of the stomach caused 558 deaths or 15.2 per cent of all deaths from cancer. This is about half the death rate for gastric cancer that many books and periodicals give.

DISCUSSION

Many text books and periodicals do not give the source of their figures for the high incidence of

gastric cancer Osler (1) gives the source of his figures but the incidence from these is only 21 per cent Ewing (4) says that the incidence of 10 per cent for gastric cancer is much too low, but more definite recent figures are not given It is well known that persons with gastric cancer tend to gravitate to medical centers, but figures from these centers are not very accurate for less serious or more easily treated forms of cancer, as breast cancer, skin cancer, etc There is some evidence appearing in Census Reports (12), that cancer of the stomach is not as frequent as some authors would have us believe The latest census report that I could find showed that cancer of the stomach and duodenum caused from 16 to 17 per cent of all cancer deaths and that cancer of the stomach is decreasing These figures are shown in Table IV These figures are much less than the often quoted 38,000 deaths annually from cancer of the stomach

The Statistical Bulletin of the Metropolitan Life Insurance Company (13), also in a recent report, shows that cancer of the stomach and liver is decreasing In the period from 1910 to 1930 the rate was 32 to 35 per 100,000, and in the period 1930 to 1940 the rate had decreased to 26 In females the death rate for gastric cancer has decreased from 32 down to 16 per 100,000 in the 30 year period This apparent decrease in the frequency of gastric cancer may be due to many factors Perhaps the most important of these is the more accurate diagnosis in the last 10 years, by more frequent and accurate X-ray studies, gastrosopic examinations, and the increasing use of surgical measures to cure or relieve obscure abdominal disease conditions As a result of these factors, cancer of the stomach has been separated from cancer of the liver in statistical reports of mortality figures Many of those in former years reported as cancer of the liver were secondary to many other organs as well as from the stomach It has been shown in a previous report (14) that peptic ulcer of the aged is often mistaken for cancer of the stomach In considering the pathogenesis of cancer of the stomach, Huist (15) has said that "Cancer of the stomach is twice as frequent in the lower social classes in England as in the well-to-do, whereas the incidence for the colon and rectum is the same" He believes that the incidence of cancer of the stomach is largely due to external factors such as poor dental hygiene, irritating or very hot foods, eating too fast, excessive use of tobacco, etc The state of Iowa may not classify as a state composed largely of the well-to-do class, yet there is not the poverty and poor hygiene and sanitation that exists in many large cities and industrial centers

CONCLUSIONS

Cancer of the stomach has been found to cause about 5 per cent of all cancer deaths in Cedar Rapids during the past 8 years, and there are about 5 per cent more cases suspected of having died of gastric cancer

Cancer of the stomach at the Hospital of the State University of Iowa, accounts for 5.3 per cent of all cases of cancer admitted there The low incidence of gastric cancer in Iowa may be affected by the high per cent of rural population, relatively little poverty, more accurate diagnosis in the data presented and other unknown factors Some evidence is presented to show that gastric cancer in the United States, is not as frequent as many authors indicate it to be

TABLE I

Gastric cancer deaths in Cedar Rapids

Diagnosed by	
Necropsy	10
Biopsy	6
Exploration	17
X-ray	13
Clinical findings	18
Doubtful findings	27
Total	91

TABLE II

Cancer deaths in Cedar Rapids by organs

Stomach	91 (12.3%)
Colon and Rectum	154
Liver	58
Pancreas	31
Abdominal	16
Uterus and Cervix	82
Breast	97
Lung	27
Others	208
Total	734

TABLE III

Cancer at Tumor Clinic, Iowa, University Hospital

July 1, 1939 to July 1, 1942	
Stomach	148 (5.3%)
Colon and Rectum	244
Liver	8
Pancreas	30
Esophagus	29
Prostate	298
Bladder	166
Uterus and Cervix	341
Breast	253
Lung	53
Unclassified	90
Others	1108
Total	2768

TABLE IV

United States Bureau of Census Report

	Year	1939	1940	1941
Total Deaths of Cancer in U S by years		153,864	158,335	159,926
Deaths from Cancer of Stomach and Duodenum, percents		26,590 17.2%	26,526 16.1%	25,953 16.2%

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A Study of the Significance and Accuracy of Cholecystographic Findings*

By

A M SERBY, M D†

and

GEMMA M LICHTENSTEIN, M D‡

CHICAGO ILLINOIS

AS members of a group for the study of diseases of the biliary tract we are interested in correlating cholecystograms with operative findings. We have reviewed the records of 278 patients, all studied with the help of cholecystograms, and operated on between 1930 and 1940.

For convenience we divided the 278 cholecystograms into 5 groups, some of which overlapped i.e.—(1) cholecystograms which showed gall stones, (2) cholecystograms which failed to show gall stones, (3) cholecystograms with no dye concentration, (4) cholecystograms with poor dye concentration, and (5) cholecystograms with fair or good concentration.

Group I Two hundred and thirty patients had cholelithiasis at operation, in 166 the cholecystograms showed stones which made the technic 72% effective. In 9 additional patients (5.1%) no stones were present at operation even though cholecystography had shown shadows which were assumed to be due to stones. The false negative shadows may have been due to gas in the duodenum or colon, fecaliths, calcified nodes or even renal stones.

Group II 103 cholecystograms failed to show stones. At operation*no stones were found in 39 instances, stones were present in 64. It is noteworthy that poor or no concentration of the dye had been reported in 54 of the 64 with stones at operation.

Group III 112 cholecystograms showed no dye concentration—68 with gall stones and 44 without gall

stones. 64 of the 68 with stones noted at X-ray examination had stones at operation an error of 6%. 36 of the 44 with no dye concentration and no sign of stones had cholelithiasis at operation. Therefore, to sum up this group, calculi were found at operation in 100 of the 112 cases. It is significant that 18 of these patients had either a high icterus index pre-operatively, or an occluded cystic duct at operation.

Group IV 89 cholecystograms showed poor dye concentration—61 with gall stones and 28 with no stones. The diagnosis in the 61 cases with gall stones proved 100% correct at operation. The 28 with no stones by X-ray examination included 18 with gall stones at operation.

Group V 30 cholecystograms showed fair or good concentration with no stones. These patients were operated upon because their symptoms were thought to warrant surgery. 20 had no stones at operation. 11 had minimal pathological changes. As might be expected, many of this group experienced little or no relief, post-operatively.*

COMMENTS

This study reaffirmed the value of cholecystography. An X-ray examination which shows gall stones with or without concentration of the dye constitutes almost irrefutable evidence of gall stones. Good concentration of the dye with absence of negative shadows denotes a normal gall bladder. If any doubt remains, the cholecystographic study should be repeated. After two or more such negative results, an

*From the group for study of diseases of the biliary tract, Michael Reese Hospital, Chicago, Illinois.

†Adjunct in Medicine, Michael Reese Hospital.

‡Clinic Physician, Mandel Clinic, Michael Reese Hospital, Chicago, Illinois.

*Find Results Following Cholecystectomy. R. B. Nettman and G. M. Lichtenstein. *Am J Med Sci*, 1944; 78: 784-1937.

operation should be performed only because the history of colics and flatulence is definite. Even then, the operation should be avowedly an exploratory laparotomy.

In all cases of doubt in which it does not appear from the history that the patient has gall bladder disease, X-ray studies showing no dye concentration should be repeated, we find, especially in our outpatient department, that the second X-ray study often turns out satisfactorily. We have learned that the failure of the first examination is usually due to misunderstanding of instructions or an inability of the patient to retain the dye. Obviously no dye will be demonstrable if the cystic duct is blocked. However, if the gall bladder is visualized, even poorly, on a second examination we may discover formerly elusive stones.

A high percentage of gall bladders which repeatedly concentrate the dye poorly or not at all contain stones. In case of doubt, the clinical syndrome dictates the decision of whether to operate or not. Repeated colics, mild or severe, may justify laparotomy. On the other hand, vague epigastric pains, dyspepsia, food idiosyn-

crasies and similar indefinite symptoms are not indications to explore in the face of poor concentration or a complete lack of concentration.

SUMMARY

1 A study has been made to determine the accuracy of cholecystographic diagnosis.

2 Gall stones were found at operations on 230 patients. Cholecystography had revealed stones in 72%. In addition, the roentgenologist reported stones in the case of 9 patients in whom no stones were found at operation.

3 In 103 patients no stones were revealed by cholecystography, but at operation 64 of the patients were found to have stones. In 54 of these 64 cases the gall bladder concentrated the dye poorly.

4 Among the group with poor or no concentration of the dye and no stones observed with the X-ray there were several persons with disease elsewhere than in the gall bladder or liver.

5 When cholecystitis is greatly suspected and the first roentgen examination is negative, cholecystography should be repeated after a lapse of a few weeks.

Abdominal Puncture—Its Value in the Differential Diagnosis between Coronary Closure and Perforated Abdominal Viscus*

By

ISIDOR KROSS, M.D., F.A.C.S.†

NEW YORK, NEW YORK

IN a clear cut case of perforated abdominal viscus or of an acute coronary closure where the clinical picture is both characteristic and unequivocal the problem of diagnosis does not come into play. Recently, however, two patients were seen at the City Hospital in whom the clinical picture was such that the diagnosis became a real problem, especially since the treatment would of necessity be radically different in these diseases. In both patients the diagnosis was easily and readily established by the use of abdominal puncture. The ease and simplicity of the procedure, the clear cut value of the findings when positive, and the apparent lack of knowledge of this procedure as evidence by its infrequent employment prompt the report of these cases in the hope that it might stimulate its use more frequently where indicated. (For details of the technique and indications for its employment the reader is referred to the publications of Dr. Bernard S. Denzer in the American Journal of Diseases of Children, August, 1920, and that of Drs. Harold Neuhof and Ira Cohen in the Annals of Surgery, April, 1926.)

CASE REPORTS

Case 1 Michael Corn was admitted to the City Hospital on the service of Dr. L. Whittemore on January 16, 1943. He had been treated previously at this hospital some seven years ago for a peptic ulcer. Since then he has been practically free from all disturbances except for very brief intervals which always passed rather quickly. His family history has no bearing upon his present condition. About one week before admission to the hospital the patient began drinking beer rather heavily and at 5 p. m. on the day before admission he was suddenly taken with severe pain and distress in the epigastrium. This was quickly followed by vomiting and sometime later by heme-temesis. The admitting diagnosis was either gastric ulcer or alcoholic gastritis. When seen in the medical ward he presented a very striking picture. He was dyspneic, cyanotic, his skin was cold and clammy, his pulse was barely perceptible and his blood pressure reading could not be obtained. The abdomen was moderately distended and somewhat spastic at the epigastrium but it did not have the so-called "board-like" rigidity. His expression was rather anxious looking. He thus presented a picture of marked shock and the diagnostic problem was a rather delicate one. Some of the staff thought that the diagnosis was acute coronary closure of a rather extensive character and

*From the Medical Service of Dr. W. L. Whittemore and the Surgical Service of Dr. I. Kross.

†Attending Surgeon—City Hospital. Associate Attending Surgeon—Beth Tarnel Hospital. Associate Thoracic Surgeon—Montefiore Hospital.

others thought that he was probably suffering from an acute intraabdominal surgical lesion such as a perforated gastric ulcer. It was quite obvious that the proper diagnosis in this case was most essential because of the radical difference in the treatment that would be indicated in these two conditions. A diagnostic abdominal puncture was decided upon and an aspirating needle was introduced to the left of the median line about three inches below the level of the umbilicus. The barrel of the syringe that was attached to the needle was pushed half way up as soon as the needle entered the peritoneal cavity as a result of the marked intraabdominal pressure. When suction was applied a highly acid, sour smelling substance was obtained in large quantities. This definitely established the diagnosis of a perforated gastric ulcer and of course definitely decided the method of treatment. The patient was now given pre-operative medication such as parenteral fluid sedation, etc. and was immediately brought to the operating room where a perforated gastric ulcer was found and where the abdominal cavity contained a rather large quantity of gastric contents.

Case 2. Simon Krupa, No 118020 was admitted to the surgical service of the writer at City Hospital on January 5, 1943. His family history was negative. About two years ago he was treated for a gastric ulcer at the Polyclinic Hospital New York City. For the past year he has noticed a definite change in his bowel habit which up to that time had been quite normal. During the past nine years the patient was suffering from cramp like pains which came on periodically at intervals of ten to fifteen minutes. During this time he stated that he had no bowel movement and that he felt quite blown up. The patient did not vomit at any time. On physical examination he did not look ill. The abdomen was slightly distended and visible peristalsis was noted. There was no rigidity of the abdominal musculature and no abdominal masses could be felt. Tentative diagnosis—carcinoma of the descending

colon. The patient was now prepared for intestinal X-ray studies. During this entire period he was ambulant. On January 10 he suddenly was taken with extremely severe abdominal pain and went into shock. He was seen shortly after this attack. His appearance was that of a man who was quite ill. He was markedly dyspneic and quite cyanotic. His skin was cold and clammy. His pulse was extremely weak and the systolic pressure had dropped down from 160 to 70. His heart sounds were very weak and quite distant. His abdomen was distended but he had no muscle spasm. The opinion of the staff was again divided. Some maintained that the patient presented a fairly characteristic picture of an acute extensive coronary closure. But in view of the previous history of gastric ulcer of two years ago and the admitting diagnosis of carcinoma of the descending colon, the possibility of a perforation of one of these viscera had to be entertained. Here again the general condition of the patient was such that an X-ray examination for free air under the diaphragm was entirely out of the question. Again an abdominal puncture was resorted to and thick, foul smelling, grayish white fluid and extremely foul smelling gas under considerable pressure were obtained. The patient was immediately given pre-operative treatment in the form of parenteral fluids and sedation and brought to the operating room. A laparotomy disclosed a peritoneal cavity filled with a large quantity of fluid and semi-solid feces coming from a perforation that was found in the hepatic flexure.

SUMMARY

Two cases are reported in which the question of diagnosis was of extreme and immediate importance and in which the treatment of the conditions considered were entirely and radically different. The use of a simple procedure such as abdominal puncture yielded the necessary information in the shortest possible time.

The Effect of Potassium and of the Cardiac Glucosides on the Vagus Reactions of the Heart and Stomach of the Turtle

By

DOROTHY FETTER, Ph D, HELEN C COOMBS, Ph D

and

F H PIKE, Ph D

BROOKLYN, NEW YORK

A GREAT deal of experimental work on the action of potassium on the physiological structures of various types of animals has been done in recent years (1) Among other effects, Zwemei and Lowenstein (2) have pointed out that in normal animals (mammals) the cardiac glucosides appear to protect against potassium poisoning, presumably by preventing a rise of plasma potassium. The object of our experiments was to extend our knowledge of the effects of potassium and a cardiac glucoside upon the simultaneous activities of two mechanisms under the control of the autonomic system, namely the heart and the gastrointestinal tract. This study is a report of the effects of potassium chloride and a cardiac glucoside (strophosid or cedilanid, Sandoz Chemical Co) upon

When electrical excitation of the vagus was done, the threshold of stimulation for cardiac inhibition and contraction of the stomach rose so high that no slowing of the heart or contraction of the stomach occurred with the maximum current obtainable. With these consistent results in mind, we studied in considerable detail with graphic records the role of the vagus in this activity, or cessation of activity. The following procedures were done.

The spinal cord of the turtle was severed close to the head by crushing the vertebral column with bone forceps. The plastron was removed with minimal damage to the attached tissues. Accumulated urine was drained off by incision of the vesical wall. Incision of the pericardium exposed the heart. A fine silk

TABLE I
Protocols

February 14 1941	Control				30 to 90 Minutes After Introduction of 2 cc of M, 10 KCl Into the Stomach			
	Stomach		Heart		Stomach		Heart	
	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus
Position of secondary coil when reaction occurred	65	5	7	No effect	—	2	6	9
					—	35	75	62
					—	—	74	70

Note. As an explanation of the numerical figures the lower the number the greater the intensity of the current employed for excitation while a high number which indicates a greater distance in centimeters of the secondary from the primary coil indicates a relatively lower intensity and therefore a higher degree of excitability of the tissues.

the reactions of the heart and gastro-intestinal tract of the turtle to excitation of the vagus nerve (1) in controls, (2) after potassium chloride, (3) after a glucoside and (4) after potassium followed by a glucoside.

In a series of twenty-five early experiments (3) in which the pylorus was not ligated, it was observed that the introduction of potassium chloride into the stomach of the turtle was consistently followed by increased intestinal peristalsis while a slight slowing of the heart rate sometimes appeared. Introduction of strophosid into the stomach in the same manner was followed by a cessation of peristaltic activity in both intestines and stomach, had any been present, although there was no change in the rate of the heart.

*From the Department of Industrial Hygiene, Delamar Institute of Public Health, Columbia University, and the Department of Physiology, University of Minnesota.

thread from the frenulum over a series of pulleys was attached to a heart lever which recorded the contractions of the heart upon a smoked kymograph. A small rubber tube was inserted into the stomach through an opening in the oesophagus and tied in place. A second small tube was inserted into the upper intestine through an incision in the duodenum and the free end led off to a tambour which recorded upon the kymograph synchronously with the heart record. Before starting an experiment, 20 cc of water were introduced into the stomach through the first tube, which was then clamped off. When gastric contractions increased the pressure, the pointer of the tambour rose and recorded the contraction upon the kymograph. The vagi were isolated well cephalad. Stimulation was done by the interrupted current from a Harvard inductorium every twenty minutes, the

TABLE II
Protocols

June 20 1941	Control				After Strophosid			
	Stomach		Heart		Stomach		Heart	
	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus
Position of secondary coil when reaction occurred	2.3	7	7.4	7	—	—	10.7	10.2
					—	—	(heart block)	ventricles stop
					—	—		

position of the secondary coil indicating the intensity of the induced current necessary to slow the heart or bring on contraction of the stomach being noted

First we considered the effect of potassium chloride alone upon the response of the organs to vagus stimulation. In fifteen experiments a decrease in threshold of the heart to vagus stimulation was shown after injection of 2 cc of M/10 KCl into the stomach. In seven we observed an increased threshold of the heart after the above treatment. In sixteen experiments the threshold of the stomach increased following administration of KCl to such an extent that the maximum current obtainable caused no reaction, while in four cases it decreased. Protocol 1 is typical.

PROTOCOL 1

We next considered the effect of strophosid alone upon the response of the organs to vagus excitation. A tenth of a milligram of strophosid (0.0001 gram) was introduced into the stomach. In twelve experiments the threshold of the heart to vagus stimulation was lowered, while the stomach threshold was increased so that in most cases no contraction was elicited with the strongest current obtainable from the inductorium.

PROTOCOL 2

When a glucoside followed the administration of potassium chloride the results show that in nine cases the stomach contracted upon vagus stimulation and the threshold returned to the original value or lower. In six cases the stomach did not show any contraction at all after the administration of strophosid.

Strophosid following potassium chloride showed no pronounced effect upon the response of the heart to vagus stimulation. Either the threshold remained the same (4 cases) or a slight decrease in the threshold for excitation occurred (7 cases).

PROTOCOL 3

In the course of these experiments we observed that the left vagus had a less pronounced effect on the response of the heart than the right. This shows in Protocols 1 and 2 in the threshold values for vagus excitation of the heart.

It is a well known observation on the autonomic system that the vagus has inhibitory effects upon the cardiac, and excitatory effects upon the gastric musculature. Potassium chloride alone, and strophosid alone, inhibit the response of the stomach to stimulation of the vagus. The action of strophosid following the administration of potassium chloride brings about a return of the response of the stomach to vagal excitation in nine cases. In six there was no effect. It may be that the two drugs unite to form a third product which increases the response of the stomach to the vagus unless the potassium chloride has had too detrimental an effect. On the contrary, the potassium chloride and strophosid separately lower the threshold for vagal inhibition of the heart. The response of the heart after strophosid and potassium chloride together is not much altered. Since these drugs have opposite effects upon the two organs to vagal excitation, the effects of the drugs cannot be on the nerve, but must take place in some structure or structures,

TABLE III
Protocols

October 20 1941	Control				After KCl				After Strophosid			
	Stomach		Heart		Stomach		Heart		Stomach		Heart	
	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus	Right Vagus	Left Vagus
Position of secondary coil when reaction occurred	10	10	10	10	2	9	12	12				
					0	0	8.5	11				
									3	11	11	11
									1	4	11	11
									1	6	13	9

beyond the nerve, e.g., the myoneural junction or the muscle

In conclusion, the above data appear to indicate that in turtle hearts rendered more excitable by excess of potassium to vagal inhibition, the irritability is unaffected by subsequent administration of strophanthidin, while in stomachs rendered less irritable to excitation by potassium chloride, the subsequent administration of the cardiac glucoside lowers the threshold for excitation by the vagus. This effect on the stomach seems to agree with Zwemer and Lowenstein's work (2)

wherein they found that cardiac glucosides prevented the typical effects of potassium poisoning

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Motor Changes Observed Fluoroscopically in the Colon of a Patient Afflicted with a Tumor in the Hypothalamic Region

By

A MAYORAL, M.D., F.A.C.R.*
NEW ORLEANS, LOUISIANA

ON October 27, 1942, M G., a 52 year-old white Louisiana male farmer was admitted to our hospital with the diagnosis of gastric carcinoma. His family history was irrelevant, his personal habits good. He had had the usual childhood diseases and an appendectomy in 1934. His chief complaints were weakness, vomiting and numbness of the hands and face.

His present illness dated from 1938. It began by extreme tiredness, weakness and severe headaches, the weakness interfering with his usual farm work. In July, 1942, he began to suffer from severe and prolonged spells of nausea and vomiting. His weakness had been progressive and forced him to discontinue work two months previously. He had been unable to walk on account of dizziness for one month.

On admission he was so weak that he had to be carried on a stretcher.

Physical examination revealed a poorly nourished male, showing no abnormal findings except a "hard mass over the epigastrium." His visual fields were normal, his pupils showed no abnormality and his reflexes were normal.

On November 31d the patient was received in the X-ray Department for a gastro-intestinal examination. This proved negative. It, however, showed no barium in the large bowel in the 6 hour film, this finding prompted a barium enema. This was asked for and done three days later. During fluoroscopic observation, great difficulty was encountered in filling the descending colon, the progress of the opaque media was very slow due to marked spasticity. When the head of the column reached the mid-transverse colon propulsive motility became very active, barium was squeezed out of the lumen toward the anus. After 20 to 40 seconds the colon would calm sufficiently to allow further progress of the enema. Each advance, however,

was met with further and similar propulsive movements of the gut. The contractions were very forcible and complete. No barium remained in the portion of intestine showing contraction except for a few flecks attached to the mucosa. In about 30 seconds these explosive movements would subside sufficiently to allow some barium to advance in the intestines. By a sort of Pilgrim's Progress the proximal portion of the colon was finally filled, but at no time during the period of observation, that lasted about five or six minutes, did the colon show complete relaxation. The movements of the colon were like those seen in cecal tuberculosis. However, the patient as far as I know had no known tuberculous focus. Amoeba was therefore suspected.

From November 9th to December 14, 1942, eleven stool examinations or cultures for amoeba and occult blood were negative. On November 16th a repeat enema was done with previous sedation. At this time no abnormality was found except for a localized area of what appeared to be thickened mucosa at the cecum.

The patient did not improve and died on December 14, 1942, of cerebral hemorrhage. No symptoms suggesting a brain tumor were recognized before death.

Autopsy about four hours after death (Dr Binford) revealed a normal gastro-intestinal tract. At once the possibility of a lesion in the hypothalamic region was suspected. Dr Binford after sectioning the brain transversely to prove the cause of death, placed it in the fixing solution and six days later found the suspected tumor. His report continues

BRAIN

The brain is dissected after formalin fixation. The posterior one-half of the right hemisphere is now a shell, the blood clot having fallen out in the fixing solution. No lesion of the corpus striatum is present.

*Chief X-ray Department U S Marine Hospital

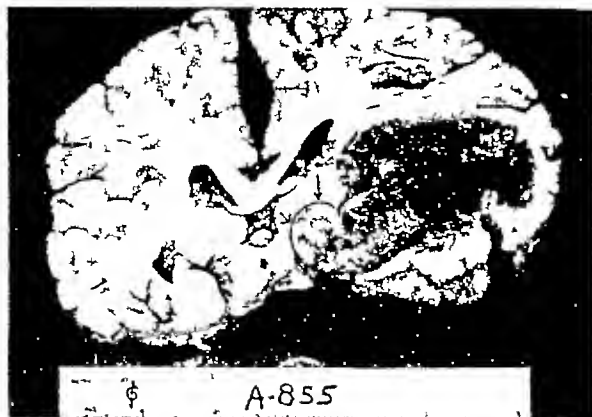


Fig 1 Gross section of brain specimen, showing intraventricular hemorrhage and site of tumor

and the anterior horns of the lateral ventricles are not abnormal. Coronal sections posterior to the mammary bodies and through the cerebral peduncles, thalamus and hypothalamus, show the gray matter medial to the inferior horn of the right lateral ventricle (gyrus hippocampus) to be the site of a poorly defined zone of opaque reddish-gray tissue within which a few small zones of clotted blood are found. The adjacent thalamic and hypothalamic regions are encroached on by this tissue. Pons and cerebellum appear normal.

Diagnosis Brain tumor (astroblastoma) right gyrus hippocampus with massive hemorrhage

COMMENT

Extensive animal experimental work and clinical observation on brain tumor patients have firmly established the existence of a brain nucleus at or near the hypothalamus having if not a selective, at least a marked influence on the gastro-intestinal tract.

Cushing (1) in his Balfour Lecture, delivered at Toronto University in 1931, furnished ample documentary data to prove that acute perforative lesion in the upper gastro-intestinal tract following the surgical removal of cerebellar tumors at or near the hypothalamus, were not accidental. While Watts and Fulton (2) experimenting on monkeys have demonstrated that "Lesions of the hypothalamic area and especially at the supra-optic and tuber nuclei are far more prone to cause profound gastro-intestinal disturbance with gastric and duodenal erosions, bleeding and even perforation than lesions elsewhere in the nervous system." Wang (3) and his associates who studied the gastro-intestinal motility on animals following stimulation of the hypothalamus anterior to the infundibular region yielded immediate blanching and occasional inhibition followed by a marked excitatory response (of the colon). Its onset was slow and gradual, and its effect lasted several minutes.

There is a wealth of material accumulated on experimental work pointing toward the relationship of hypothalamic region and the gastro-intestinal tract. With the exception of Wang's experiment however, all deal with hemorrhage and erosion. This case is

therefore unique in that at no time there was hemorrhage, occult or visible, and in that ulceration of the mucosa was not found at autopsy, nor evidence of old scars seen. All changes were motile.

There is, however, a complicating factor in this patient, he died from hemorrhage into the right ventricle. It is a known fact that injection of certain substances (solution of pituitary, by Cushing) (4) will cause gastric hypermotility and reverse peristalsis, and by inference one might suspect other segments of the gastro-intestinal tract. Although I find no recorded observation on the relationship between gastro-intestinal action and hemorrhage into the ventricles, it could be suspected that the hemorrhage into the ventricle that caused his death either by distention of the ventricles or by mere presence therein may have some influence on the gastro-intestinal function. To dispel this possibility, I especially

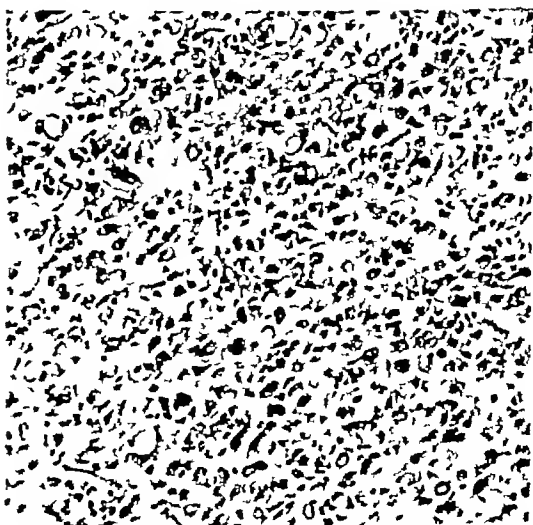


Fig 2 Photomicrograph of brain tumor showing pleomorphism. Weigert's iron hematoxylin and van Gieson stain $\times 95$

questioned Dr Binford who assured me that the hemorrhage was recent, that there was no evidence of old hemorrhage and in his opinion it did not exist on November 6, 1942, the day on which the altered motility of the colon was observed, one month and eight days previous to his death. Stimulation of the pituitary gland by the tumor, causing hyperactivity could also be suspected, but review of the anatomical location place it too distant from this gland to warrant the suspicion. Histological study of the pituitary does not reveal hyperactivity. The bulk of evidence seems to be, therefore, that the motor disturbance seen was solely due to the action (mechanical or otherwise) of the tumor on the hypothalamus.

This case is being reported because I believe that even an inexperienced observer could not have overlooked the altered motility shown by my patient's colon. Motor disturbances of all of the gastro-intestinal tract in the presence of stimulus, experimental or, by lesions on or near the hypothalamus seem proven. Motility of the tract above the colon is so often and easily disturbed by so many other causes, that so far as I know, by itself, it is of no special value in diagnosis. The colon is a sluggish lazy organ. Motor disturbances are unusual and if future observations reveal repetition of the observations described herein, they will assume a positive value, and may be of aid in suggesting the existence of silent brain lesions touching the hypothalamus. The findings to be emphasized are exaggerated colon motility propulsive, over a large section of the colon. In the presence of blood in the stool, occult or otherwise, the absence

of specific ulcerative lesion of the gut, such as tuberculosis, amoebic or bacillary dysentery, must be ascertained before brain tumor is suspected. I need not stress the difficulty of such differentiation.

After reading the extensive literature dealing with tumors and other lesions in and about the hypothalamic region, and the relationship between these lesions and gastro-intestinal regulation, I feel that we cannot form an opinion on a single opaque enema examination. The response to stimulation seems to be intermittent, although how often, no experimenter is ready to assert. It seems to me that those of my colleagues who are working in tumor clinics where large groups of brain tumor patients are assembled could throw light on the subject by frequent fluoroscopic examinations of the colon of large series of patients with known brain tumor, especially if at or near the thalamic region.

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Gastric Secretion and Sugar Metabolism

By

CHARLES L GLAESSNER, M D
NEW YORK NEW YORK

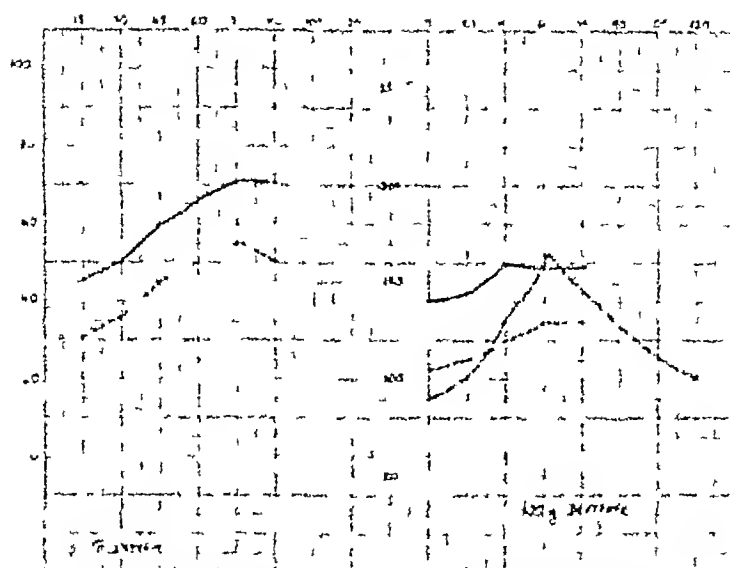
MAY I draw your attention to some less well known but important phenomena in the relationship between the absorption of sugar and gastric secretion.

The idea that a relationship between blood sugar level and gastric acidity does exist, is by no means a new one, although discussed in the literature for more than 10 years no unanimity of opinion concerning the character of these ties has been reached. Three groups of experiments will be discussed, which shed some light on the intimate relations between sugar metabolism and gastric acidity. These are (1) The effect of insulin upon gastric secretion, (2) The effect of hydrochloric acid—administered in the duodenum—upon glycemia, (3) The inhibitory action of intrajejunally administered glucose upon gastric acidity.

(1) *The insulin-acid complex*. Since the experiments of Okada, La Baire, Kalk-Meyer and others, we

know that insulin is one of the most potent stimulants of gastric secretion. Each lowering of the blood sugar favors the secretion, each increase of the level diminishes it. La Barre and his coworkers observed that insulin strongly stimulates gastric secretion and motility in dogs. They supposed that the rise of secretion was due to hypoglycemia. Neither parenteral increase of the blood sugar, nor increase produced by the administration of adrenalin are capable of inhibiting this effect. Further studies revealed that resection of both vagi inhibited the secretagogue action as did also the administration of atropin (parasympathetic effect). Phlorhizin which does not cause hyperglycemia, was without antagonistic effect. Not only does the acidity rise under the insulin whip, but the water, the mucus, the secretion of sodium chloride are also intensified. In confirmation of what I have already said it is interesting to note that in diabetics

*Read before the Virchow Medical Society New York May 3rd 1943



——— total acidity - - - - - free hydrochloric acid
 glucose in the blood (blood sugar)

Fig 1 J. P. Normal Reflux

HCl 40—35—50—55—50

TA 45—50—60—55—50

After 100 gms glucose intraduodenal

HCl 22—25—30—35

TA 42—42—50—45

Blood sugar 90—100—100

Marked reduction of both the free acid and of the total acidity
 Sugar resorption in normal limits

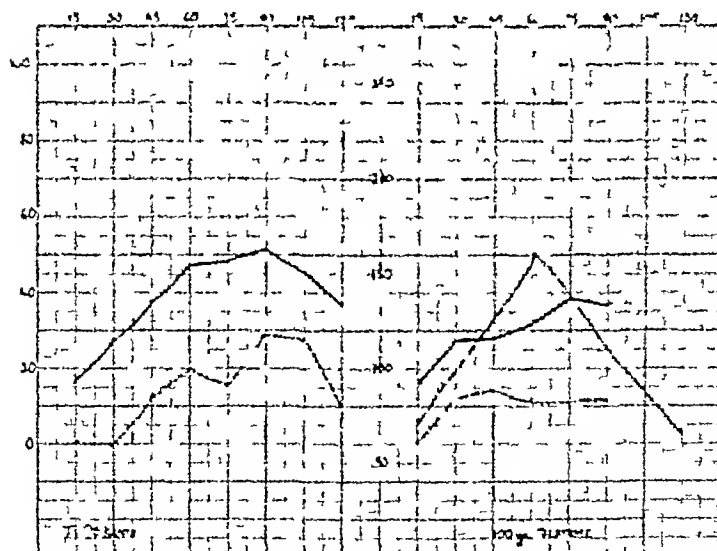


Fig 2 F. S. Normal Reflux

HCl 0—0—12—20—16—30—28—8—30

TA 16—26—36—46—45—50—50—36—38

After 100g glucose intraduodenal

HCl 0—14—12—12—12—12

GA 16—28—28—22—35—35

Blood sugar 70—170—75

Marked inhibition the blood sugar curve is elevated

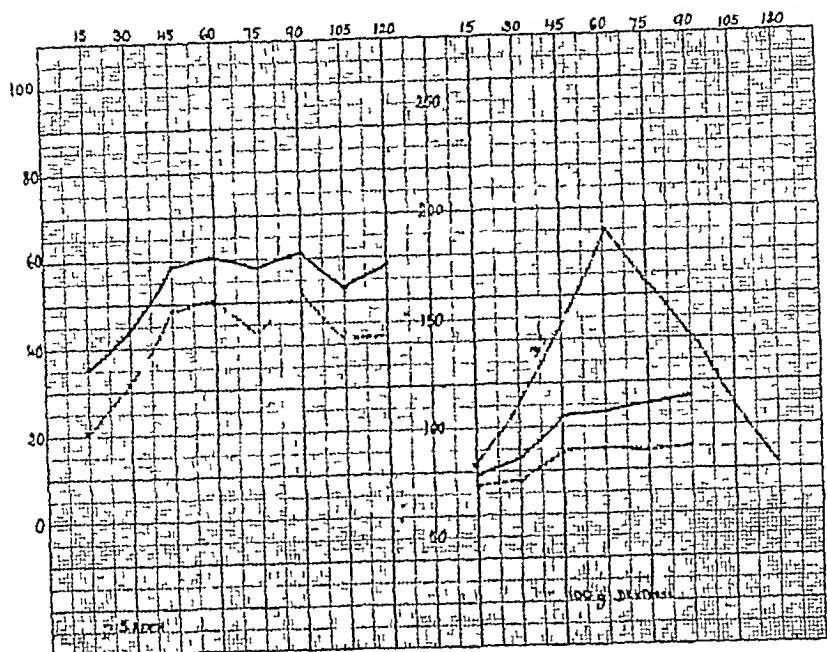


Fig 3 S R Normal Reh fuss

HCl 20—32—48—50—44—52—42—44

TA 34—44—58—60—58—60—54—58

After 100g glucose intraduodenal

HCl 8—10—16—16—28—20

TA 12—14—24—24—26—28

Bloodsugar 85—175—80

Inhibition marked, the glycemia is slightly higher

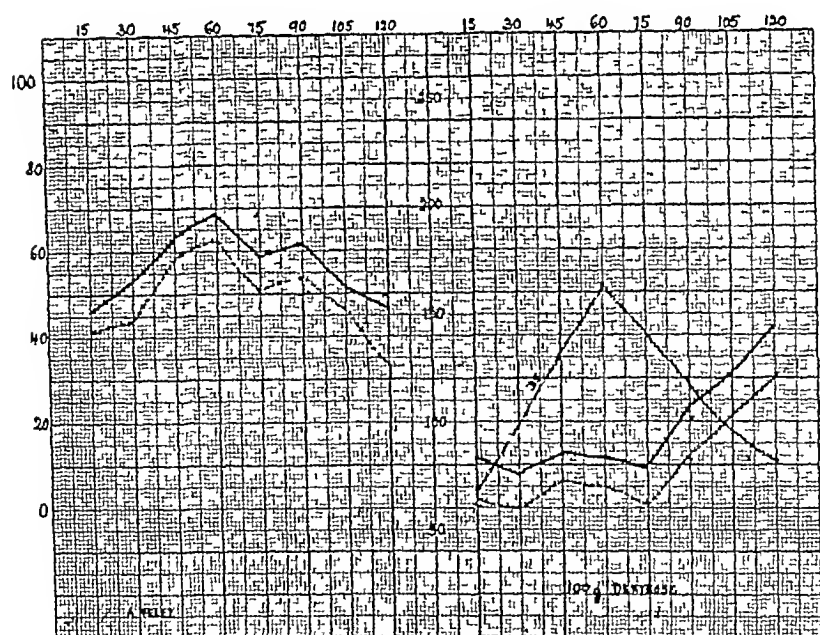


Fig 4 A V Normal Reh fuss

HCl 36—38—58—62—46—50—46—34

TA 42—48—64—70—60—62—54—48

After 100g glucose intraduodenal

HCl 4—2—8—6—12—24—32

TA 12—8—14—14—24—32—48

Bloodsugar 65—165—80

In this case the inhibition is obvious, the sugar curve slightly elevated

the acid effect of insulin is not evident until hypoglycemia causes normal hyperacidity and hypersecretion. There are also some very interesting relations between hunger and hypoglycemia which were reported by Hofstein, Henning and others and are to be noted. In ulcer cases hunger and hunger pain run parallel, the hunger pain in duodenal ulcers starts in the night, at the time of maximal hypoglycemia. These findings correspond with the observation, that whilst in normal individuals gastric secretion ceases during the night in ulcer patients there is a permanent secretion, most pronounced during the period of most marked hypoglycemia (as determined by blood tests during sleep). Mention must be made of the fact that not all observers in the field are in agreement on this subject. Boldvress and Stewart could not confirm the formula hypoglycemia and gastric secretion. It was further observed that acid secretion started immediately after the onset of hypoglycemia, but that maximal hypoglycemia was reached a considerable time afterwards. This finding led to the explanation by Fiels-Piero, Iv, Popesco, Dobress and others that a diphasic action of insulin probably takes place: the first phase is inhibitory and the second stimulating.

Finally Lapp-Dibold showed that a normal gastric secretion could be observed during the hypoglycemic phase of a sugar meal. Blood sugar 66 mg %, HCl 45. Total acid 50. Whereas hypersecretion and hyperacidity could be observed in the same patient after insulin injection with the same blood sugar level as before. Blood sugar 68 mg %, HCl 110. Total acid 116. They therefore denied the specific secretagogue action of hypoglycemia.

It is difficult to reconcile these observations. Much remains unknown. However one must take into consideration the fact that insulin produces other effects besides that of its action upon sugars. Insulin is a polypeptide and included in its actions therefore, may be the secretagogue action common to polypeptides. In spite of any experimental criticism I should like to repeat that three very striking facts speak in favor of the sugar theory of the insulin acidity. (1) The fact that the diabetics show no rise of acid until they become hypoglycemic. (2) The observation that the secretion starts with the onset of hypoglycemia. (3) The experience that sugar parenterally administered is not capable of replacing the glucose destroyed by insulin. The action of the liver is necessary.

It seems that the glucose administered by intravenous injection is infused too slowly or in insufficient quantity or that the passage through the liver for reasons not yet known to us, is necessary or that the glucose is eliminated rapidly by the kidney. At any rate we know that insulin is a powerful secretagogue of the stomach, the action is caused probably by hypoglycemia and can be inhibited by the enteral administration of glucose. The manner in which insulin produces its effects is probably by stimulation of the vagi and also by thalamic and hypothalamic actions.

Atropin is an effective antagonist, histamin and pilocarpin are supporting drugs.

(2) *The question of the action of acid on the intestine* has not aroused the same interest as the insulin effect but nevertheless merits attention. If hydrochloric acid in physiologic concentration is introduced into the duodenum, hypoglycemia results. The basic experiment was performed by Freud-Nazim who introduced 100 cc of 0.5% hydrochloric acid into the duodenum of dogs and observed a rapid fall of blood sugar. These experiments were confirmed by Zunz, La Barre-Hazard in animals, by Olivero and Conti in man. The hypoglycemia resulting from the introduction of acid was attributed by these authors to the freeing of insulin. However it was later known by La Barre and others that this phenomenon also occurred in depancreatized dogs and therefore could not be dependent on the freeing of insulin. It has been known for some time that secretin-like ferments or hormones have insulin-like qualities and the explanation for the development of hypoglycemia on the introduction of acid into the duodenum probably lies in the freeing of these secretin-like ferments. Such hormones or ferments can be found in the duodenal or jejunal walls. When we suppose that the mere presence of hydrochloric acid in the small intestine acts on the blood sugar level then we confirm the close relationship that exists between acid and sugar metabolism. The effect of small medical doses of hydrochloric acid may therefore be explained in the following manner. Small doses of the acid entering the duodenum free insulin-like ferments which produce hypoglycemia. The hypoglycemia in turn leads to insulin hyperacidity thereby achieving the end result.

(3) The third problem deals with the *inhibitory action of intrajejunally administered glucose upon gastric acidity*. In many ways it is the most interesting. Experiments with intrajejunally administered glucose were performed years ago by Kalk-Meyer and others, but this question has not been yet examined systematically. Matsuyama distinguished two phases of gastric secretion: the psychic and the chemical, each of which reacts differently towards glucose-administration into the duodenum; the psychic phase can be inhibited by parenteral sugar administration, the second phase not. Matsuyama believes that the inhibition is due partially to the excitement of sensory fibres. The thalamus and hypothalamus are the centres of the inhibitory action. Similar experiments were performed by Komarov-Dav. These authors found reduced secretion of gastric juice in prolonged hypoglycemia. Intravenous but to a greater degree intraduodenal sugar administration, inhibited the gastric secretion. The same effect could be observed in sham-feeding and after histamine-injections. Phlorhizine was without effect. The resection of the vagi, the elimination of the thalamic and hypothalamic areas interrupted the inhibitory action of sugar.

Experiments in man confirmed the inhibitory action of sugar. Christlieb gave glucose per os and obtained

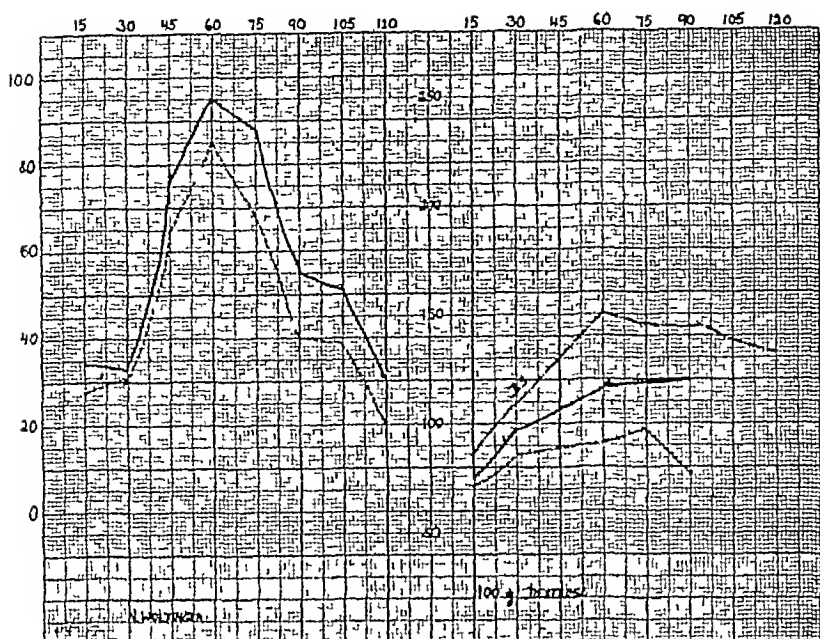


Fig 5 N W Normal Refhuss
HCl 28—20—64—84—68—40—38—20
TA 38—36—76—96—86—54—52—30

After 100g glucose intraduodenal
HCl 6—12—14—16—20—12
TA 16—20—24—30—30—30
Bloodsugar 85—150—135

Very spectacular inhibition, the sugar curve is delayed

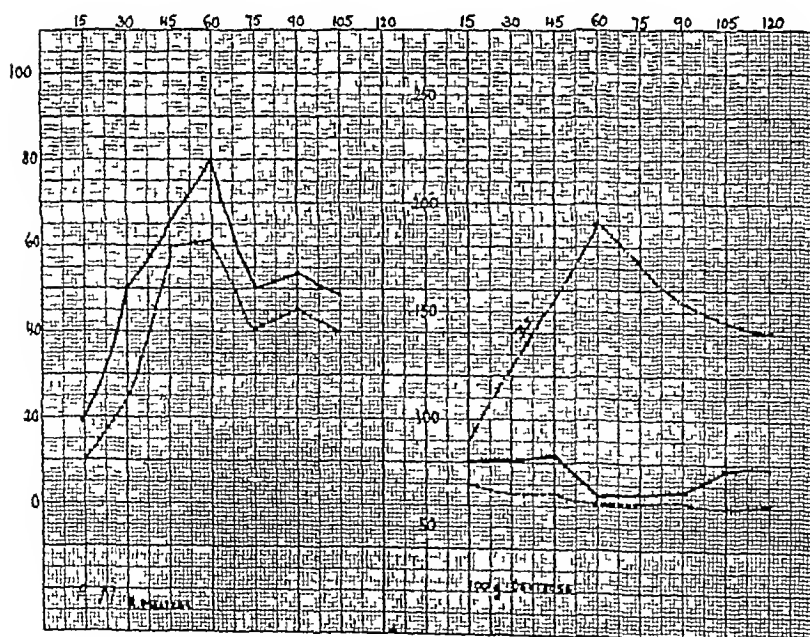


Fig 6 R M Normal Refhuss
HCl 10—24—60—60—40—44
TA 18—50—66—80—50—54

After 100g glucose intraduodenal
HCl 0—8—12—12—10—10—6
TA 10—16—20—22—14—16—10

Bloodsugar 90—190—140

Marked inhibition, high bloodsugar curve

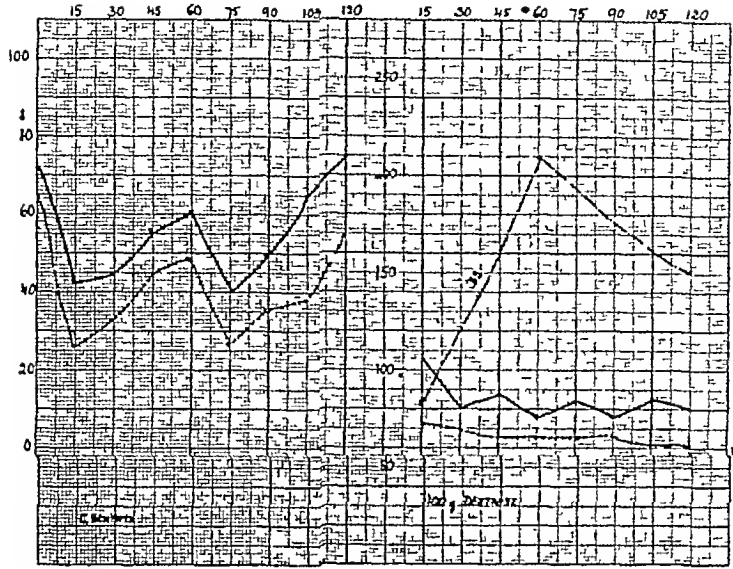


Fig 7 G S Normal Refluss
HCl 64—24—32—46—48—26—36—38—54
TA 74—42—44—56—60—40—50—64—74
After 100g glucose intraduodenal
HCl 6—2—2—2—2—2—0—0
TA 26—8—14—8—12—8—12—10
Bloodsugar 78—212—150

The inhibition is spectacular, the bloodsugar curve high

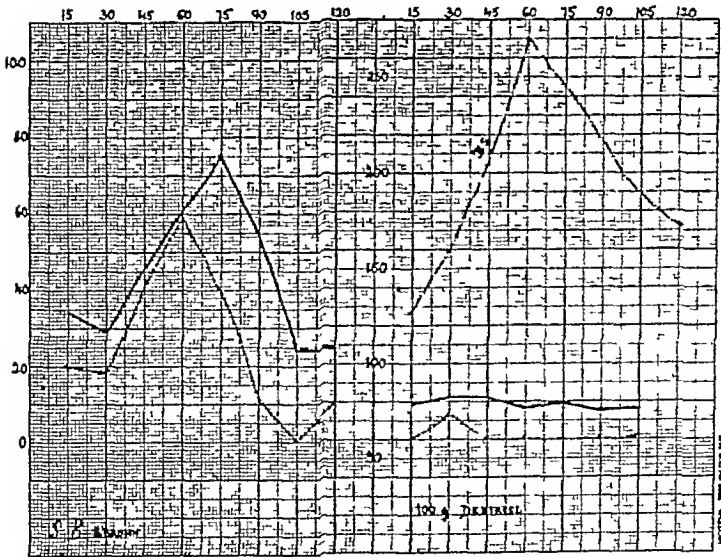


Fig 8 S B Normal Refluss
HCl 20—18—46—60—40—12—0—10
TA 34—28—58—76—56—24—24—20
After 100g glucose intraduodenal
HCl 0—8—0—0—0—0—0—0
TA 10—12—12—10—10—8—8—8
Bloodsugar 125—270—170

Both the inhibition and the bloodsugar curve are spectacular

varying results. However, since the sugar solution diluted the gastric juice, these experiments were not at all convincing. Kalk and Meyer must be considered the first who introduced glucose into the duodenum; they found considerable inhibitory effects.

Our own experiments, which I performed in cooperation with Dr. A. Winkelstein*, concern 8 cases of different gastric diseases. These observations were plain in the conception. The gastric acidity was determined by the Rehfuess method; the following day the fasting blood sugar was determined and then 100 Gms. of glucose in 300 cc. of water was administered into the duodenum with a duodenal tube. After this feeding the tube was withdrawn into the stomach and a Rehfuess test again performed. 30 minutes after the sugar administration and again 2 hours later the blood sugar was determined. The right position of the tube was controlled in every instance.

We see in these 8 cases a progressive inhibition of the acid-secretion in the stomach after the intrajejunal administration of 100 Gms. glucose. In the last 3 cases a real anacidity occurs. Studying the blood sugar figures we note the very close connection between blood sugar and degree of inhibition of acid secretion. There is no doubt that acid inhibition runs parallel with hyperglycemia. The problem that poses itself now, is the following: We are not able to produce inhibition by parenteral (intravenous) only by the intestinal administration of glucose. The reasons for this peculiar finding may be: (a) That we cannot introduce a large enough quantity of sugar by the intravenous method. (b) That the intravenously administered glucose leaves the body rather rapidly. It is difficult to obtain a high enough concentration in this manner. (c) And this is the most likely, that the passage through the liver parenchyma is essential in

*Gastro-Enterological Department of the Mount Sinai Hospital, New York

order to produce the inhibitory effect of glucose and even other sugars (levulose, galactose) upon gastric secretion. The exact mechanism of this action is not known. This newly discovered relationship between liver function and its control of gastric secretion merits our closest attention. It opens new pathways of study which may yield interesting and even important results.

Studying the curves of our 8 cases we see that free and bound acid run parallel, that the curve of acidity mirrors the curve of the sugar-level. The higher the latter, the greater the inhibition.

But also clinical problems could be based on our arguments: the lack of ulcers in diabetics, 0.25% in diabetics, 1.5% in total, 33.3% of achlorhydrias in diabetics, 4-6% in total (Wohl); the incidence of ulcers in healed or controlled cases of diabetes. The occurrence of hunger pains in ulcer cases during the night, when the hypoglycemia is at its highest level, the powerful activity of insulin upon gastric secretion at a stage when the blood sugar is at the lowest level, at a stage when hypoglycemia occurs.

But not only scientific problems arise, purely practical ideas may be mentioned: the feeding of ulcer-patients via duodenum by glucose in high concentrations and quantities has to be tried. Such experiments may be performed via sugar drip or via jejunal tube.

Our three questions elucidate the relations between sugar metabolism and gastric secretion. The insulin action upon the stomach, hypoglycemia and gastric secretion. The hypoglycemic action of acid introduced into the small intestine and finally the inhibition by intraduodenally administered glucose of the gastric secretion. We see in those problems a very important connection between gastric secretion and sugar metabolism, in which the liver function also surely plays a very important role.

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Notes On Nutrition

Feeding the American Soldier The quality of the fighting man's morale depends to a large extent on the quality of his food. The Quartermaster Corps conducts a Subsistence Research Laboratory. The Medical Department has a Nutrition Branch. The National Research Council has a Subcommittee on Medical Nutrition, of which Dr. James S. McClester is Chairman. Field Ration A is nutritionally balanced, provides ample variety and fully utilizes seasonal fresh fruits and vegetables. Type C ration consists of previously prepared food packed in six hermetically sealed cans, 3 of which contain a meat and vegetable stew or hash, and 3 biscuits, sugar and soluble coffee. The "5-in-1" Ration consists of canned evaporated and dehydrated foods in quantities sufficient to supply 5 men for one day. The Task Ration is carried on the soldier's person. The Type K pocket Ration is packed in 3 durable cartons which together weigh about two pounds, and consists of biscuits, canned meat or cheese, a confection, and beverages different for each of the three meals, as well as chewing gum and four cigarettes, providing about 3,000 calories. In planning rations, such questions as comfort after eating, thirst provoking qualities and the character of the stools are considered. The average soldier eats nearly 4,000 calories a day.

Vitamins and Fatigue Persons suffering from deficiencies of the Vitamin B-complex tire easily, although when this complex is fed to normal persons no increased vigor is noted. Hard physical work necessitates an adequate intake of the Vitamin B-complex, without which fatigue and a specific type of muscle ache and joint pain develops. Thiamine alone helps but is not in itself enough to prevent these symptoms or the physical deterioration which follows hard work on a diet inadequate in the B-complex (J Nutrition, 24:585, 1942). Again, just because adequate vitamin intake of all kinds is essential to the vigor of men doing hard work, it does not follow that a diet superabundant in all vitamins will produce in working men an excessive or superabundant energy, and this has been shown by experiments with soldiers (J Nutrition 23:259, 1942).

Available Iron in Foods The percentage of the total iron which is available for hemoglobin formation is the "available iron," and is roughly equal to the amount of iron of the food which will react with α -dipyridyl. Many researches carried out using the dipyridyl method have at least shown one point of importance—that copper is necessary for the utilization of iron for hemoglobin. Also, they have indicated that iron from animal sources is higher in available iron than from most vegetables. However, in trying to determine the effects of drying, or canning on the available iron, there are intrinsic difficulties

which seem to cast doubt on the findings. One of these is that the grinding of dried foods usually may be assumed to have added new iron from the blades of the grinder (J Biol Chem, 103:61, 1933), (Food Research, 7:503, 1942).

Nutritional Status of a Population Group in Madrid A clinical and laboratory study of 561 persons living in a Madrid suburb in 1941 showed that the chief deficiencies, apart from total calories were animal proteins, eggs, cheese and fruits, with lack also in calcium. Vitamin A and riboflavin. Weight loss and macrocytic hyperchromic anemia were common, and the chief disease found was tuberculosis (at least 13 out of 521). Probably permanent physical and mental handicaps will follow the food shortages occasioned by war in most countries of Europe (J Nutrition, 24:557, 1942).

Niacin for Angina Pectoris Although the amide of nicotinic acid in the form in which the vitamin appears to occur in food, has no untoward effects, it has been observed that the administration of the free acid, niacin, may be accompanied by facial flushing, hot flashes and sweating. This effect has been studied in connection with the treatment of angina pectoris, with rather startling results, although the treatment ought not to be carried out except under adequate hospital conditions. From 100 to 300 mg of niacin in the form of a 0.05 per cent solution is administered by drip infusion. Six such infusions are given during the course of about three weeks. Six persons so treated showed complete cure of symptoms over periods of from 3 to 7 months and three persons were able to resume heavy work. This effect of niacin is considered to be a more or less pharmacodynamic action and holds promise of future development (Lancet, II:419, 1942).

Physiology of Pantothenic Acid Analogues Pantothenic acid is required for the growth of mammals and microorganisms. Several analogues of pantothenic acid have been prepared and tested for their bacteriostatic action. One of these—pantothaurine, was found to possess highly inhibiting qualities for various bacteria (Biochem J, 36:364, 1942), (J Biol Chem, 139:975, 1941).

Dietary Protein and Absorption of Calcium By feeding constant, rather low amounts of calcium to men, but varying the protein in the diet, it was shown that in the presence of a high protein intake, 15 per cent of the calcium was absorbed as compared with an absorption of only 5 per cent in the case of a low protein diet. This probably means that the amino-acids facilitate calcium absorption. As a result, in persons or races in which calcium intake is low, a high protein

diet may convert the calcium deficiency into sufficiency (Biochem J, 36 686, 1942)

Some Problems of Nutrition in Aviation Some of the medical problems of aviation devolve about airsickness, the special problems of the obese and the expansion of intestinal gases at high altitudes (War Medicine 3 1, 1943) A light bland meal two hours before flight has been found best so far as airsickness is concerned The fat of the obese person can store large amounts of nitrogen and this gas appears as minute globules when high altitudes are reached, thus making the obese flier more subject to "the bends" In all fliers there is the likelihood of gas expansion at high altitudes, and ridding the tract of gas depends on swallowing less air, (carbonated drinks, gum chewing, air swallowing to adjust the Eustachian tubes to ascent, etc, etc) Food should be high in protein, moderate in carbohydrate, rather low in fat, and the meals are best given every 4 hours in order to prevent hypoglycemia The Vitamin A content should exceed 10,000 IU daily for visual reasons

The American Diet Several food surveys of foods eaten by Americans in various localities in every one of the various income brackets have resulted in the following conclusions (1) In all brackets ignorance is an even greater factor than poverty in choosing inadequate diets, (2) There seems to be no indication that more than 2 per cent eat too little meat, (3) Probably most persons are slightly low in thiamine, (4) Most diets are rather low in green and yellow vegetables, fruits, milk and eggs, (5) Lack of riboflavin and thiamine is the most common vitamin lack, (6) Among minerals, calcium and iron are the most common deficiencies None of these studies correlated the physical condition of the persons investigated Even physicians did not choose better diets than others in the same income brackets

Soils, Crops and Better Nutrition. Only recently have agricultural scientists concentrated their attention on improvement of the nutritive quality of farm products Literally hundreds of thousands of agricultural experiments which have been conducted in the various agricultural experimental stations since 1887, when they were established, have neglected this point in favor of increased quantitative production But now since 1938 when Congress made additional funds available, regional laboratories have been established for the study of factors affecting the nutritive value of farm products It has been found that tomatoes, cereals and turnip tops, as well as other products, may show an extreme variation in their vitamin content, sometimes as much as 50 or even 100 per cent The starting point of good crops is good seed Climatic conditions are even more important than soil conditions Ascorbic acid content may be increased by increasing the length of the exposure to fluorescent light

The Biological Activity of Various Forms of Vitamin A Generally speaking, four times as much caro-

tene is required than Vitamin A for physiological needs of most animals

Thiamine in the Infant's Diet The infant's only source of thiamine is milk. Human milk contains less thiamine than cow's fresh milk, or even boiled cow's milk Evaporation of milk causes a considerable loss of thiamine Probably infants' feeding formulas should be enriched with crystalline thiamine under certain conditions (Am J Pub Health, 32 1013, 1942)

Collaborative Study of Riboflavin Assay Methods The American Chemical Society are in process of establishing an accurate method for riboflavin assay Both fluorimetric and microbiological methods are being used and agree one with the other More is required to make riboflavin assay perfectly satisfactory (Ind Eng Chem Anal Ed, 11 346, 1939), J Biol Chem 131 621, 1939), (Cereal Chem, 20 3, 1943)

Unusual Foods of High Nutritive Value In Hawaii the guava juice and the fresh solo papayas are being used for children because of their high Vitamin C content The rutabaga approximates the citrus fruits in its ascorbic acid content The black currant and especially the wild rose hips are also high in ascorbic acid Some wild roses, especially those growing in Northern latitudes, as Russia, may contain as much as 14.6 per cent of the dry material as ascorbic acid Some Canadian investigators have confirmed this and found also that the leaves of the evergreen are high in ascorbic acid The wild rose crop of Alberta alone is estimated at half a million tons, with an estimated supply of 5,000 tons of ascorbic acid Such findings point a solution to our own supply as well as a supply for the peoples of conquered countries after the war (Canad Med Ass'n J, 48 30, 1943)

Diet and Hepatic Tumor Formation Of the many types of experimental diets now available to investigators, those most susceptible of dietary modification appear to be the hepatic tumors due to butter yellow (p-dimethylaminoazobenzene) Rats fed certain deficiency diets, such as a mixture of rice and carrots, readily develop liver tumors when the dye is added to the ration, but if a protective food is fed in addition, the effectiveness of the dye is reduced and the incidence of the tumors is significantly lowered Casein and riboflavin are among the more important of these inhibiting factors No clinical deductions of course can be made as yet from these experiments (Cancer Research, 699, 1941)

The Farmer's Wartime Feeding Problem The farmer is faced by the request to reproduce increased quantities of food, animals and eggs, but he is faced also with certainty of serious shortages in feeds, especially feeds high in protein The present processing mills for soybean cannot take on bigger amounts for processing, even though the soy crop is doubled, and soy bean cannot be fed as such without processing Bone meal will be short, as well as milk, and some

vitamins may be lacking, although Vitamin D can be taken care of by activated yeast and activated 7-dehydrocholesterol (J Am Vet Ass'n, 102:217, 1943)

Growth of Children The growth of all young animals depends very much on the quantity and quality of their food. Even Vitamins E and K and choline, usually not thought of as important in growth, make a difference by their prolonged absence from the diet. The long period of human immaturity, as well as the influence of heredity and racial characteristics, make it difficult to plot an ideal graph for children's growth. Extensive measurements of Toronto school children showed that in recent decades children are taller and heavier than they used to be, and that the taller are more intelligent. Children of professional men are taller and those of unskilled laborers, unemployed, pensioned and retired classes are shorter. Wetzel's "grid" method indicates that each individual has a growth pattern of his own, and all children may be classified as obese, stocky, good, fair, borderline and poor. Periods of nutritional insufficiency may be reflected in a distortion of the theoretical graph of an individual. Growth may be retarded by bacterial disease, postural defects, etc. So far as nutrition is concerned vitamins ought not to usurp complete attention, for calories, proteins and minerals also are important. (Dept Trade & Commerce, Dom. Bur of Statistics, Social Analysis Branch, A Height and Weight Survey of Toronto Elementary

School Children, Ottawa, Canada 1939 (1942), (J. A. M. A., 116:1187, 1941))

Polyn neuritis Caused by Thiamine Deficiency In monkeys and in man it has now been shown that polyn neuritis is a manifestation of thiamine deficiency. It is a manifestation of late rather than early, and severe rather than mild thiamine lack. In earlier experiments it is now known that the initial deprivation of thiamine was so severe as to cause death before the development of objective polyneuropathy. (Arch Int Med., 71:38, 1943)

Ascorbic Acid in Milk Commercial raw milk may contain 21 to 23 mg of ascorbic acid per liter, and pasteurized milk about 16 mg per liter. The vitamin occurs in milk in two forms—reduced ascorbic acid (Vitamin C) and oxidized ascorbic acid (dehydroascorbic acid). The latter is unstable and on further change loses its character as a vitamin. Heating and presence of copper promotes the accumulation of the oxidized form. In view of the fact that citrus fruit is not easy now to obtain, one should remember tomatoes as well as milk. A quart of milk may supply a substantial part of the daily minimum requirement of 35 mg of ascorbic acid. (J Dairy Sci., 26:7, 1943)

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Editorials

THE NUTRITIONAL BASIS OF MORALE

MORALE is as essential in civilians as in soldiers. It is courage, determination and the sustained will in action. It depends partly upon physical and mental inheritance and education, but also upon the nature of the diet of the individual. Deprive even a courageous man of thiamine for three months and he becomes irritable and tired while the addition of this vitamin factor to his diet brings him back to normal in a few weeks. The basis of morale is neither purely physical or spiritual, but both—it is, in short, psychophysical. It is the duty of many agencies in society to inculcate ideas which arouse and maintain morale. It is the duty of medicine and the science of nutrition to understand and encourage those physical measures which build and express courage, and form the physical basis upon which the will can act.

The most valuable experiments in human nutrition would be those carried on over a large arc of the life cycle. Since it is difficult to enforce a diet on any person or any people for a long period knowledge may more easily be obtained by the study of groups who are known to have followed certain types of diet over many generations. For example, we know that the Chinese diet, for many hundreds of years, has

been largely one of rice, yet the stamina of the Chinese Army and the Chinese civil population during the past six years of war became one of the astonishing facts of modern history. Of course there has been a definite philosophical and racial mood behind this, especially that *patience* about which the West knows little from its own experience. One might wonder how a national diet of rice could support the expression of such sturdy qualities in time of peril. It must be remembered that the rice in China, for forty centuries, has been grown on a highly cultivated soil enriched perennially with the products of human excrement. Since no better fertilizer is known, and since the seeds from one crop of rice became the seeds of the next crop, a continuity of breed was established. This rice seed of China may safely be regarded as among the "aristocracy" of seeds. They are pedigreed agents capable of passing on to each successive generation all benefits of constant excellence of soil and all benefits of a straight line of natural mutation. It is safe to assume that rice grown from such seeds possesses nutritional advantages far beyond any breed accidentally transported from one soil to another soil or from one climate to another climate. For 4,000 years the Chinese farmer held his little division of land

under the Tsing Tien system in fee from the government. The land, immune from sale or mortgage, was his to make or mar, and he made the best of it. However, it is true that the Chinese private soldier of today, subsisting on rice and a few vegetables grown at random, cannot stand either infection or extreme fatigue as well as the American soldier whose diet is the subject of expert nutritional study and control. But from his ancestors, the Chinaman has inherited a body which reflects the advantages of a racial diet grown on highly fertilized soil.

It should be borne in mind that in America today the most perfect diets are those of our armed forces. How many people in America during the decade preceding the war partook of a diet as perfect as that now used in the U. S. Army? The answer is that extremely few persons, even among those in whom ignorance was not a factor, managed to eat a perfect diet. Recent investigations of the American diet are alarming in the deficiencies which exist—especially in milk, ascorbic acid, thiamine, riboflavin, calcium and iron. Much of the fault is due to ignorance, but some of it may be attributed to the fact that agriculture as a whole, even today, has not seen the importance of improving the nutritive quality of crops, but still aims at increased quantitative production. This ideal, as well as increasing absentee landlordism, has resulted in insufficient fertilization of the best type, with loss of humus and subsequent land impoverishment. No one knows how much this "soil sickness" is to be credited for increase of certain forms of human disease or defects in human morale. Perhaps we shall never know. But when we become alarmed by certain social tendencies, such as the shrinking sense of individual responsibility in politics, laziness of the population and the virtual disappearance of the American home, we ought to remember that nutrition must play an essential role in building public morale, and that agriculture eventually must be given an incentive beyond humanitarianism for the production of quality crops.

Our government, since the Morrill Act of 1862, has moved ever nearer toward an eventual realization of the ideal of nutritive crops. Countless experiments have now been carried out at agricultural stations on soils, fertilizers, farm animals and the influence of climate on crops. Scientists are now aware that through the ideal of quantity production much is being lost in the actual quality of the foods. Maynard, of the U. S. Plant, Soil and Nutrition Laboratory at Cornell University, states that it is as essential to consider the yield of essential nutrients as the total tonnage of the crop. It has been found that different samples of a given cereal may show as much as 100 per cent variation in thiamine content. Equal variations in the calcium and phosphorus of timothy may be found. Apples may show a 50 per cent variation in their Vitamin C content. It is known that so far as the recognized food essentials are concerned, the climatic, geographic, temperature and rainfall factors are of greater importance than the chemical environ-

ment of the plant root system. As Maynard contends, the starting point of good crops is good seed. He believes that it may never be possible to buy pedigreed vegetables or cereals, with a soil or climate certificate attached, but he relies on public education to bring these basic truths into action. As Nutrition Reviews states—"It should now be possible to correlate genetic, chemical, physical and climatic factors with the physiological production of plant compounds of value in human and animal nutrition, in a manner that has not been possible heretofore. Scientific workers will watch with interest this new experiment in the expenditure of public funds in a more carefully controlled study of the various factors affecting the nutritive value of farm crops."

This problem of improved human nutrition through quality crops must be placed where it belongs, in the hands of scientific investigators. The idea has made a vast appeal to many categories of persons, some of whom have attempted methods of farm revolution which will not work. During the past decade, many European refugees have tried to propagate here and in Canada certain methods of fertilization which cannot be attempted on a large scale at present. The chief recommended fertilizer was a "natural compost" made from excreta, dead leaves, branches, twigs, timothy, and, in fact, almost anything organic, except artificial fertilizers. Some of these persons were under the primary influence of Steinerism or had observed the Steiner methods as used in England. Their proposals usually fell on deaf ears because of a fear that their story was merely a new "ism" without much behind it. A farmer could not be induced to strive to raise carrots containing unusual amounts of vitamins and minerals at a premium cost price, simply because there was no way to be sure of a premium selling price. Some of these European enthusiasts have settled down on small farms which they bought for the purpose of conducting their experiments on a smaller scale.

A study of Steiner's agricultural teachings strikes the American as a strange mixture of authoritarianism and tradition, without the necessary scientific demonstration to support it. The work of G. T. Wrench, M.D., of London, is not so easily disposed of. His book (1) appeared in 1938, and described a very healthy people who live in the Native State of Hunza, in the mountains at the border of Afghanistan and the Chinese Empire. This book was reviewed in this Journal in January, 1939, and there was something of a protest from several sources, because unless one had read the book himself and was certain of Wrench's *bona fides*, he would be unprepared to give credence to what the book revealed. One letter from a prominent internist said in part—"It seems a waste of time to review a book which obviously has been written by one of those slightly crazy doctors who cause so much trouble in society." This letter represented a total misunderstanding of Wrench's sincerity and a failure to see the potential importance of what Wrench had

written Wrench was sufficiently sane that the British Government early in 1939 heavily subsidized his work and that of his colleagues, directed toward revolutionary methods of farming. The war has interrupted but has not ended the valuable work to which Wrench and others in England have devoted themselves. The book itself, while very much in line with recent trends in American scientific agriculture, was chiefly a record of the health experience of the Hunza people over a long period of time and it was supported by McCarrison who previously had noticed the unique health of this people who differed from their neighbors only in the matter of diet. Briefly the Hunzas have no illness of any kind, and their old men of 70 play polo and retain the characteristics of youth. "It is proved fairly conclusively that this happy state of unique physical fitness is to be attributed solely to their diet. The latter is low in meat, but rich in dairy products, whole grain cereals, germinating seeds, fresh vegetables, abundance of freshly picked fruit and freshly fermented wine. This diet, it will be seen is high in protective substances, and resembles the ideal diet of McCollum and Simmonds although the latter did not contain wine. The limitation of varieties at any one meal is rather a new conception save for the teaching of certain American food faddists, which have not received the sanction of the profession. This all sounds like a simple prescription in view of the fact that the people who eat it and because they eat it, fail to furnish any of the exhaustive catalogue of diseases which adorn the repertoire of the European and American practitioner. Not even appendicitis? No, not even a single spastic colon, and no concession to the Western luxury of allergy. What a benighted race indeed! But as Dr Wrench quickly points out, it is not quite so simple as it appears. As usual there is a catch in it. Just as the reader has seized a pen to make a list of the Hunza diet (which might be used on himself if not his patients and procure for him a prolongation of his mortal itinerary) a difficulty looms up. These fruits, vegetables, cereals and germinating seeds are intangibly different from ours because they are the products of mountain terraced farming and each edible product today has a history through its seeds—a history in Hunza of the most expert agricultural tradition, in which soil fertilization is attained by the special use of special composts. It is almost inferred that the plain love of agriculture is not unconnected with the brilliant food results long attained in this mountain nation" (2).

The book suggested that any group of people who could raise crops of this kind over a period of time would gradually gain in health and perhaps like the Hunzas be without disease. Of course faith is not enough. The entire subject must be painstakingly investigated. From the data which Wrench presents, his conclusion is justifiable. The Hunza diet is the one factor which differentiates this people from neighboring nations — neighbors who unfortunately are as prone to disease as we are. This fact has been verified by McCarrison clinically and through animal

experiments, using the Hunza diet on one group of animals and the diets of the neighboring nations on the control animals. This group fed the Hunza diet remained free of disease whereas the others had all the diseases to which the animals were subject.

Psychosomatic medicine gradually is impressing the apparent truth that man is a unity, incapable of intelligent dissection into body and mind. Morale and stamina are characteristics of individuals who enjoy proper teaching and proper physical food. Whether the Hunza formula is the final answer to the nutritional problem or not does not matter. At present it must appear to American nutritionists however that we as a people can reap ideal nutrition only through a new idealism in agriculture, embracing the large idea of raising crops on the basis of their nutritive content and not their gross weight. As everyone is aware, farmers cannot be expected at once to take up such a task. Pedigreed seed and ideal grains and vegetables are something that lie in the distant future. Even if it were proved beyond doubt that Wrench is correct in his magnificent assumption and that perfect health awaited only the inculcation and practice of perfect eating, there are a thousand vested interests ready to militate against so radical a conception.

But when a new and potentially big idea based on the general good manages to become clearly defined there will always be found men of courage who will risk misunderstanding and ostracism to push it over. There will also be found men of a different strain who will use it for racketeering purposes. Today American agricultural scientists and American nutritionists both see the tremendous issues at stake. However progress must be slow. Anyone who wishes can make the experiment within limits in his own back yard. Everyone can at least understand that our national morale once the war is won, will require buttressing. Renewed efforts to attain perfect nutrition do not represent the sole need of America, but they represent a *sine qua non* in the process of postwar remodeling. The path appears to be through the educational work of agricultural scientists.

Berumont S. Cornell

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ERROR

In the article "Digestion and the Nervous System" which appeared in the June issue of this Journal, the author J. Earl Thomas, M.D., wishes to make a correction. On page 202, first column 15th line, it reads "Carlson verified these results and showed that excitatory responses were obtained most frequently when the muscle was in a state of contraction or possessed

Chronic Peptic Ulceration of the Oesophagus

By

E. E. CLEAVER, M.B.*
TORONTO, CANADA

PEPTIC ulceration of the oesophagus has been considered a rare condition but a careful study of the medical literature reveals the fact that several groups of cases have been reported.

Friedenwald in 1929 reported 13 cases verified by oesophagoscopy and radiological examination. This author believes that a short oesophagus and a diaphragmatic hernia have been overlooked as a definite factor in the production of peptic ulcer of the oesophagus. In his opinion, a short oesophagus is an unlikely complication of ulcer of the oesophagus caused by inflammatory reaction and scar tissue formation, since in the majority of cases it is present with diaphragmatic hernia as a predisposing factor. It was further shown that a continuous bath of free HCl will produce an ulcer in the absence of gastric mucosa. Seven patients did well on Sippy management without local treatment except dilatation.

Chevalier Jackson reported 88 cases in 1929, 21 active and 67 healed ulcers found in 4,000 consecutive cases, in which oesophagoscopy was performed for diseases of the oesophagus. He found evidence of increased patency at the cardia but he made no report on radiological findings.

Chamberlain reports 7 cases of ulceration of the oesophagus. He demands certain diagnostic criteria: (1) The ulcer must be unassociated with systematic disease. (2) The ulcer must be seen at oesophagoscopy or at autopsy. (3) Free HCl must be present. (4) The ulcer must be chronic. (5) Symptoms must be relieved by ulcer therapy and dilatation.

Lyall discusses the clinical features of peptic ulcer of the oesophagus. The clinical symptoms are Pain, Haematemesis, Dysphagia.

Pain. Generally commences in lower end of the sternum, sometimes in the epigastrium. It may radiate from point of origin in epigastrium upwards to the sternum, round to the back and to the left supra-clavicular region. Pain is often due to the passage of food over ulcerated area. Pain in the lower end of the oesophagus usually appears immediately after the swallowing of food if it is due to spasm but it may appear as a late symptom two to three hours after meals, simulating gastric or duodenal ulcer.

Haematemesis. Rapid fatal hemorrhage is usually due to erosion of the aorta. More commonly there is intermittent vomiting of coffee ground material or frank blood.

Dysphagia. In early stages often dysphagia is slight and the food seems to stick momentarily and then pass on. In later stages when fibrous stricture

appears the condition becomes more severe and finally complete.

Complications

(1) Perforation may occur into the pleura, pericardium or bronchus.

(2) Acute mediastinitis. This is an uncommon complication and is due to spread of infection from the base of the ulcer into the surrounding tissues.

A very clear and comprehensive discussion of Peptic Ulcer of the Oesophagus has recently been presented by Dick and Hurst. These authors had the opportunity of studying 16 cases since 1933. Radiologists have recognized herniation of the stomach through the oesophageal hiatus, which results from congenital shortness of the oesophagus but it has been generally thought to be of little clinical importance. The morbid anatomy of chronic peptic ulcer of the oesophagus differs in no way from that of chronic gastric and duodenal ulcer. Ulcers are usually situated in the lower third of the oesophagus and generally above the sphincter. The size varies from a small lesion a few millimeters in diameter to one completely encircling the lumen. Small ulcers are round and oval. Large ones tend to be irregular and are often annular. The wall is penetrated to a variable depth with exposure or perforation of muscular wall. The usual course in oesophageal ulcer is to heal completely.

Pathogenesis. Complete healing may occur without any obstruction developing but stenosis of varying degree frequently results. Dick and Hurst are of the opinion that gastric juice gains access to the lower end of the oesophagus as a result of regurgitation through an incompetent cardia, associated with a short oesophagus and much less frequently due to secretion by islands of ectopic gastric mucosa in the oesophagus.

The following cases of Peptic Ulcer of the Oesophagus have been observed and studied in the public and private wards of the Toronto General Hospital.

Case 1. Mrs. H. A woman of 68 years complained of lower sternal pain for four months. At first pain commenced from a half to one hour after meals and continued until relieved by food or an alkali. Later pain became more severe, radiating to the back and to both shoulders and associated with a feeling of soreness in both arms. A slight hemorrhage had occurred just before admission to hospital and several small hemorrhages had occurred during the next few days. A week later the patient brought up a cupful of blood.

Oesophagoscopy. Small chronic ulcer seen in the

*Department of Medicine, University of Toronto

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continued for a few minutes. At this time pain was localized to lower end of sternum but later the pain increased in severity and radiated to throat and down both arms. Pain frequently was increased on lying down. There was no haematemesis.

Oesophagoscopy by Dr. Giegler McGiegor showed a chronic ulcer two inches above the caecia. There was no ectopic gastric mucosa.

X-ray showed narrowing of the lower three inches of oesophagus with some dilatation above the stricture and herniation of the stomach was noted. Duodenal feeding was employed and later dilatation with

two inches above the caecia. Biopsy reported ectopic gastric mucosa.

Treated with duodenal feedings. No dilatation was done. Patient remained well for six months. Peptic ulceration of the oesophagus, confirmed by biopsy, but no diaphragmatic hernia and no short oesophagus were seen.

Case 6 Mrs S. Age 60. This woman gave a history of dysphagia over a period of five years. The first attack occurred in 1939. Following this short attack the patient was free of symptoms for a year. Since 1939 the attacks of dysphagia have become more frequent.

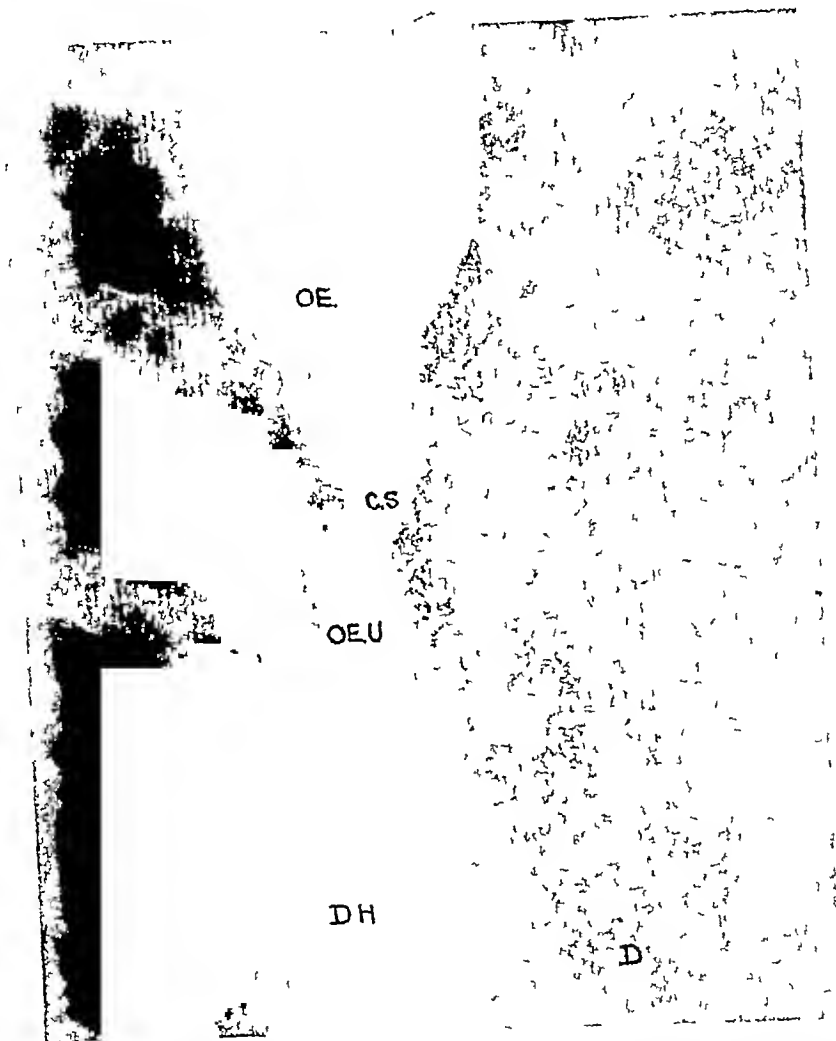


Fig 2, Case 3 Short oesophagus and diaphragmatic hernia. Annular defect three inches above caecia. OE — Oesophagus, DH — Diaphragmatic hernia, OE U — Oesophageal ulcer, CS — Cardiac sphincter.

Jackson's bougies. Considerable improvement was noted.

Case 5 Mrs S. Age 42. In November, 1942, this woman vomited a small quantity of red blood on two occasions. No history of pain. No dysphagia.

X-ray at this time showed no evidence of ulceration in the stomach or duodenum. Some irregularity of the lower end of the oesophagus. No ulcer or varicosities noted. No diaphragmatic hernia seen. No short oesophagus was present.

Oesophagoscopy showed three small ulcers about

Patient is troubled with mucus. It is necessary to clear the mucus before food may be taken. There has been no severe pain but she complains of a burning sensation extending from the epigastrium to the throat. There has been no haematemesis.

Oesophagoscopy. Dr A. H. Veitch reported an indurated chronic ulcer 13 inches from the teeth. Oesophagitis was noted above the point of constriction.

X-ray findings. Obstructing lesion in the lower third of the oesophagus. Within the lesion is a small protrusion which represents a small ulcer. This lesion is regarded as malignant, yet the clear cut appearance

is not typical of carcinoma. Diaphragmatic hernia and short oesophagus are present. The presence of an ulcer in the oesophagus, although no ectopic gastric mucosa is present and the X-ray findings of a short oesophagus with a diaphragmatic hernia, suggests the diagnosis of peptic ulcer. Malignancy of the oesophagus persisting for four or five years is unlikely.

Treatment with dilatation has improved the dysphagia. There has been a slow but steady increase in weight.

Case 8 Mrs. McK. Age 60. This patient gave a history of difficulty in swallowing since a child. Later she had frequent spells of vomiting and dysphagia when in training as a nurse. Shortly after confinement the dysphagia became more acute and in September, 1911, she was unable to swallow even clear fluids for three days. Pain was a minor symptom. X-ray showed a stricture at the level of lung root and extending for a distance of about three inches. Slight dilatation of oesophagus proximal to stricture. Herniation of the

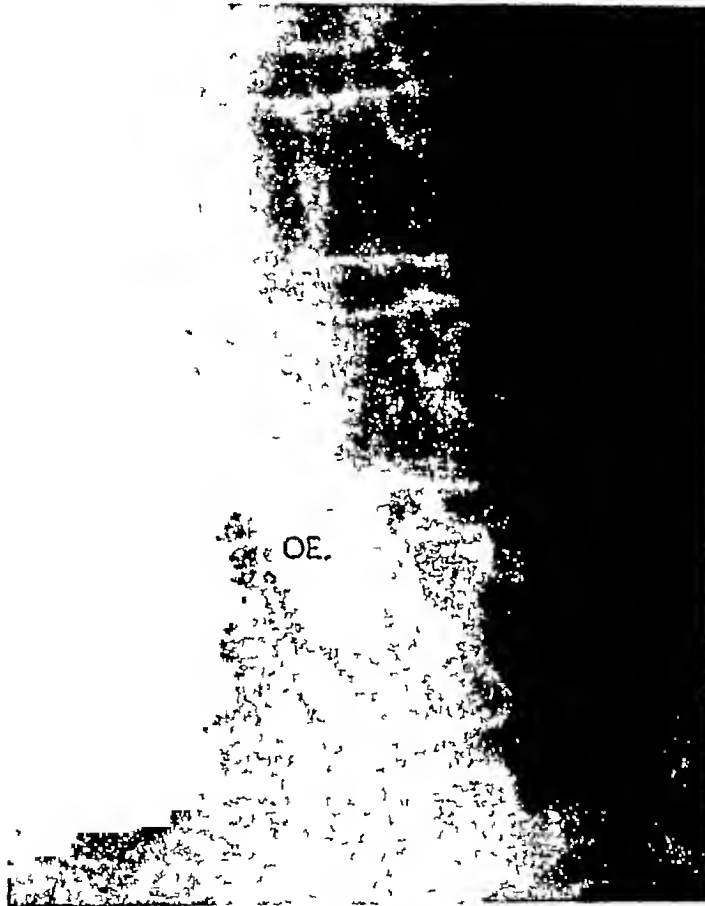


Fig 3, Case 5. No diaphragmatic hernia. No short oesophagus. Oesophagoscopy—3 small ulcers and ectopic gastric mucosa. OE—Oesophagus, D—Diaphragm.

Case 7 Joseph D. Age 46. This man gave a history of mild dysphagia for 12 years and severe dysphagia even for fluids during the past few months. He did not complain of pain.

Oesophagoscopy. The lower end of the oesophagus, 14 inches from the teeth, was distinctly narrowed and a healed ulcer was seen.

No biopsy was done.

X-ray showed a marked spasm in lower and of the oesophagus with an associated small ulcer.

The clinical history, positive oesophagoscopy and X-ray findings made a diagnosis of ulcer of the oesophagus probable.

stomach noted with a short oesophagus. No ulcer crater was demonstrated.

Oesophagoscopy examination in November, 1941, showed a stenosis, twelve inches from the teeth. A definite small ulcer could be seen at the point of stricture. Biopsy showed chronic inflammation but no evidence of ectopic gastric mucosa. Jackson's bougie No. 30 was passed readily. Subsequently Jackson's bougie was passed frequently with temporary relief. A duodenal tube was also easily passed and the patient improved markedly and gained in weight. The course has not been entirely satisfactory. This patient frequently has dysphagia which is temporarily relieved.

by dilatation. The history in this case dates from childbirth and the writer has formed the opinion that some injury was inflicted on the oesophagus as a child, which did not become a major disability until after her confinement. The cause of ulceration cannot be definitely determined but the finding of an ulcer in the lower end of the oesophagus, associated with herniation of the stomach and a short oesophagus, strongly suggest a peptic ulcer of the oesophagus.

Case 9. Mrs G. Age 62. This woman first had choking spells seventeen years ago. Attacks of dysphagia were infrequent until two years ago when dys-

oesophagus with diaphragmatic hernia and ectopic gastric mucosa.

Case 10. Edward L. Age 79. This patient complained of difficulty in swallowing over a period of a year. The dysphagia had been slowly progressive. There was no history of pain or hemorrhage.

Oesophagoscopy. In the lower end of the oesophagus, 13 inches from the teeth, a large bleeding ulcerated area, denuded of mucous membrane was seen. Biopsy showed a fibrous exudate with chronic inflammation. There was no gastric ectopic mucosa.

X-ray showed partial obstruction at juncture of the

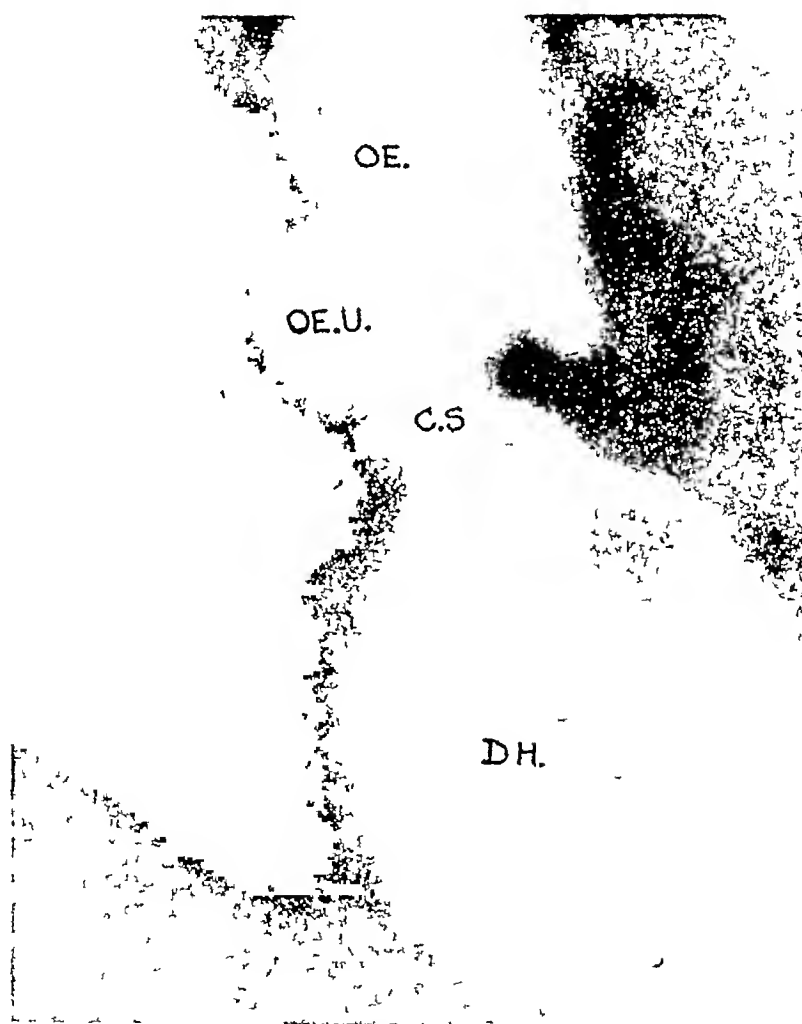


Fig 4, Case 6. D—Diaphragm, DH—Diaphragmatic hernia, OE—Oesophagus, CS—Cardiac sphincter, OE U—Oesophageal ulcer.

phagia became more frequent. Since December, 1942, she has had increasing difficulty in swallowing of solids. She complains of a grasping pain at the upper end of the sternum which is relieved in a few minutes, either by the relief of the spasm or by induced vomiting.

Oesophagoscopy. A simple ulcer was seen 13 inches from the teeth. Biopsy reported ectopic mucosa.

X-ray findings. Stenosis of oesophagus 2 inches above the cardia. No definite ulcer. A short oesophagus and diaphragmatic hernia were present. This case is the only one in our series that shows a short

middle and third of the oesophagus. The constriction was half an inch in length, with dilatation above it. A small hernia through the oesophageal hiatus was seen.

DISCUSSION

In this series of 10 cases, there were 5 males and 5 females. The ages were 68, 41, 67, 48, 42, 60, 46, 30, 62 and 79. Pain was a definite symptom in 7 cases. Pain generally commenced in the lower sternal region, sometimes coming on a half to one hour after meals and relieved by taking food or an alkali. Pain was often described as a burning sensation behind the

sternum. The pain was often worse when the patient was lying down. Pain was sometimes associated with regurgitation of acid mouthfuls. Again the pain might radiate to the back, to both shoulders and sometimes down one or both arms. Pain of a burning character was sometimes felt when patient bent forward. Pain not infrequently was of the peptic ulcer type, might be present daily for several weeks and then disappear for weeks or months. Pain at first occurs when hard solids are taken. Very hot or cold drinks, acids, condiments, etc., frequently produce pain. The duration of the pain may vary from a few

frequent. Pain according to patient has only been present since January 1943.

Hemorrhage is generally not an early symptom but usually occurs following a long history of pain and dysphagia. Occasionally bright red blood or coffee colored material is regurgitated. In the later stages a profuse hemorrhage may occur and sometimes may prove fatal. Severe anemia frequently results from a large hemorrhage or repeated small hemorrhages. Definite haematemesis occurred in three cases. There was no hemorrhage in seven cases.

X-ray findings were positive for short oesophagus

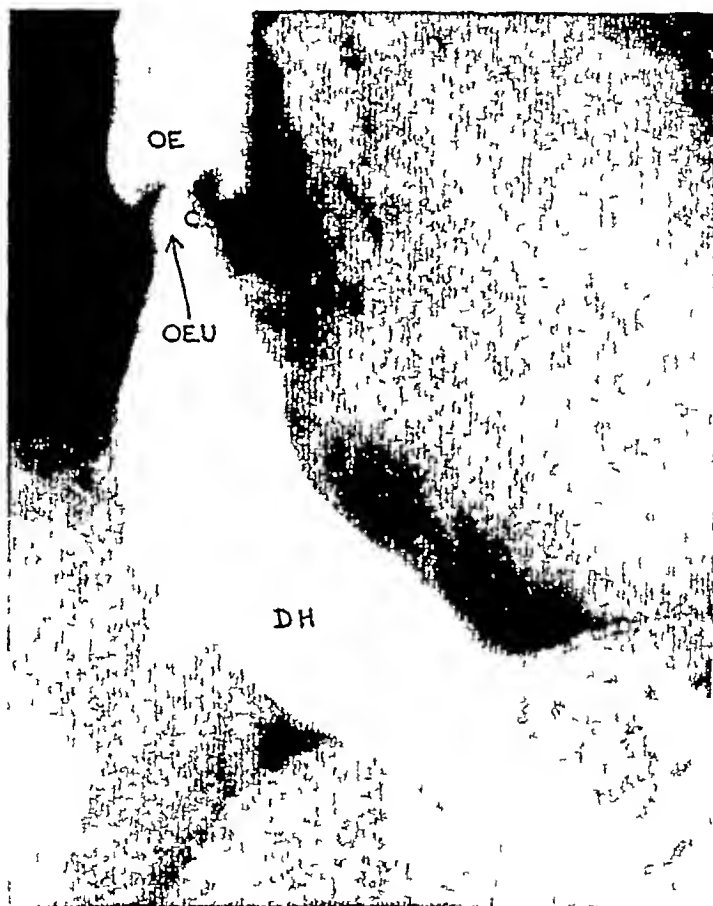


Fig 4A, Case 6. Another view of the same case as shown in Fig 4.

minutes to hours unless relieved by alkalis or antispasmodics.

Dysphagia may be present from the onset of the disease but generally develops after the pain has been present for some months. This symptom is not present until obstruction develops. The obstruction may be due to either spasm or actual stenosis or both. Great distress may be experienced if stenosis is complete and patient is unable to belch gas from the stomach into the oesophagus. In one case reported a woman of 62 had suffered with choking spells for fifteen years. During the last ten years attacks of dysphagia were

and diaphragmatic hernia in seven cases. Oesophagoscopy was done in eight cases. In two cases biopsy showed ectopic gastric mucosa. One case had both ectopic gastric mucosa and the short oesophagus associated with a diaphragmatic hernia. The other case showed ectopic gastric mucosa but no short oesophagus.

DIAGNOSIS

The clinical history in peptic ulcer of the oesophagus is often difficult to differentiate from gastric and duodenal ulcer. The burning pain behind the sternum, worse when the patient is lying down and especially

when the pain radiates to the shoulders and down either one or both arms, makes the diagnosis of ulcer of the oesophagus probable. When oesophagoscopy shows an ulcer and the X-ray reveals a short oesophagus and a diaphragmatic hernia, the diagnosis is established.

Cardiospasm or achalasia generally is associated with a long history, regurgitation of large amounts of mucus and food and usually there is absence of pain.

Carcinoma of the lower end of the oesophagus usually gives a history of early dysphagia and obstruction.

short oesophagus, the oesophageal ulcer will be in contact with the acid contents of the stomach at certain times when the cardiac sphincter is incompetent. Fluids and semi-solids should be taken at two or three hour intervals. Hot or cold fluids should be avoided. Solids generally cause discomfort and pain. The patient is more comfortable in the sitting posture during the day and the head of the bed should be raised at night to prevent the regurgitation of the acid contents into the lower end of the oesophagus. If this plan is not followed, frequently the patient complains of a burning pain in the lower end of the oesophagus.

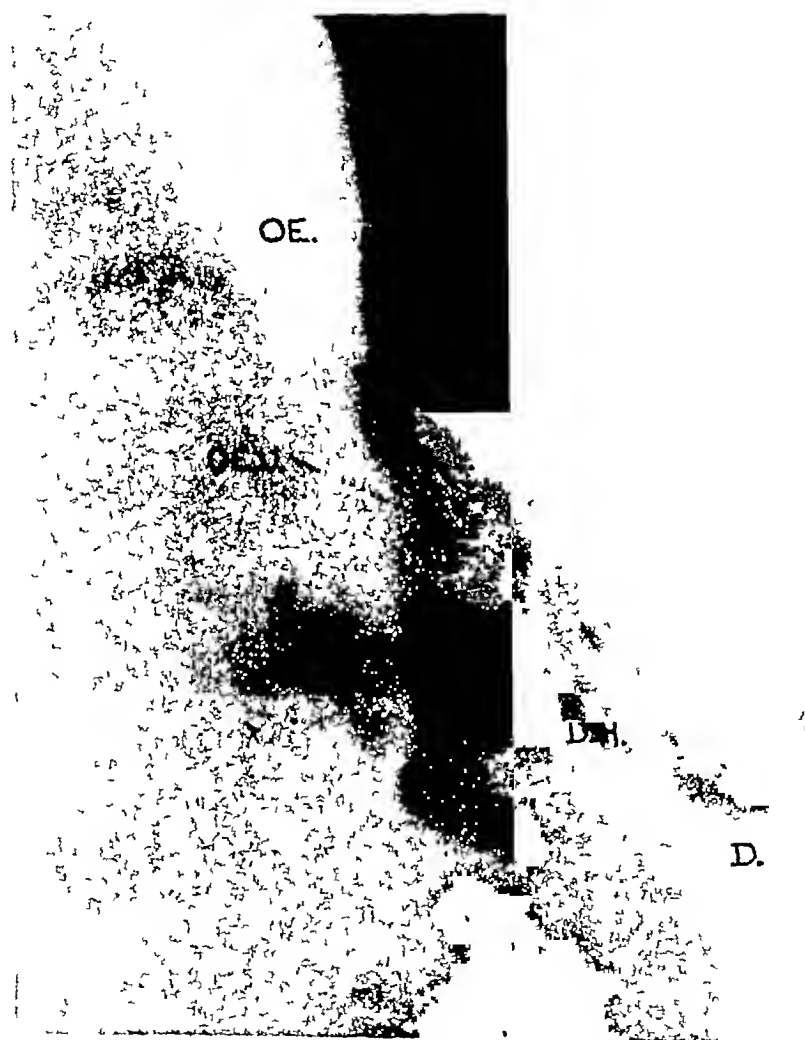


Fig 5, Case 7 OE—Oesophagus, OE U—Oesophageal ulcer, D H—Diaphragmatic hernia, D—Diaphragm

Pain generally occurs late in the disease. The X-ray appearance is generally characteristic. Biopsy from the edge of the ulcer usually decides the diagnosis.

Short oesophagus and diaphragmatic hernia without ulceration seldom give rise to symptoms.

TREATMENT

When the X-ray shows no diaphragmatic hernia and no short oesophagus, but biopsy shows an ectopic gastric mucosa, the treatment of ulcer of the oesophagus is the same as for gastric and duodenal ulcer, but when the X-ray reveals a diaphragmatic hernia and a

that often radiates to the neck, shoulders and to the arms. Tincture of Belladonna in doses of 15 to 20 minims should be given fifteen to twenty minutes before each feeding. The dosage should be increased by 5 minims daily, until dryness of the throat or disturbance of accommodation occurs. A tablespoon of mineral oil should be taken before each feeding. An alkaline mixture is sometimes helpful. The author has found that feeding by duodenal tube is very satisfactory. The tube is generally readily passed into the stomach and six or seven feedings of milk, orange

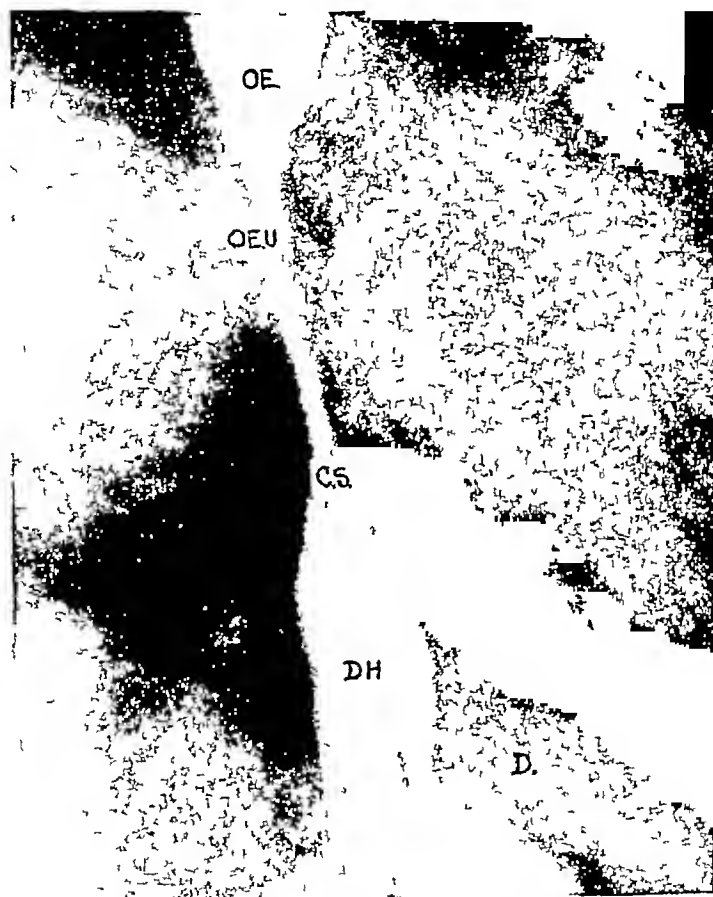


Fig 6, Case 8 D—Diaphragm, DH—Diaphragmatic hernia, OE—Oesophagus, CS—Cardiac sphincter, OEU—Oesophageal ulcer

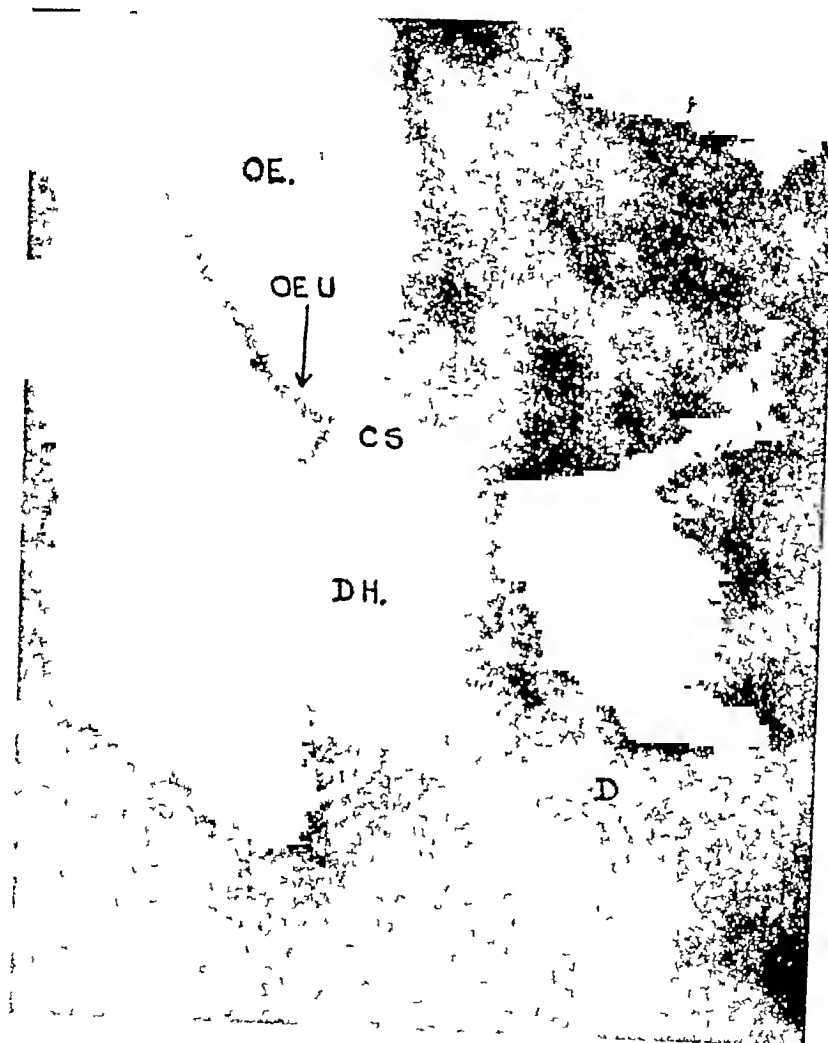


Fig 7, Case 9 D—Diaphragm, DH—Diaphragmatic hernia, OE—Oesophagus, CS—Cardiac sphincter, OE U—Oesophageal ulcer

juice, liver extract, corn syrup and ascorbic acid should be given in twenty-four hours. The patient experiences little discomfort and the necessary requirements of nutrition are met. The presence of the duodenal tube assists in maintaining the lumen of the oesophagus and may prevent the development of marked stenosis or stricture. After the patient has been fed with the duodenal tube for three weeks, if any difficulty in swallowing is experienced, dilatation is necessary. Hurst mercury tubes sometimes relieve dysphagia but frequently it is necessary in order to

SUMMARY

Peptic Ulceration of the Oesophagus is not a rare disease and presents a definite clinical picture, with positive radiological findings.

It is nearly always associated with a congenitally short oesophagus and a diaphragmatic hernia which permits regurgitation of the acid contents of the stomach into the oesophagus.

In one case the acid secretion of ectopic gastric mucosa was the probable cause in the development of oesophageal ulcers.

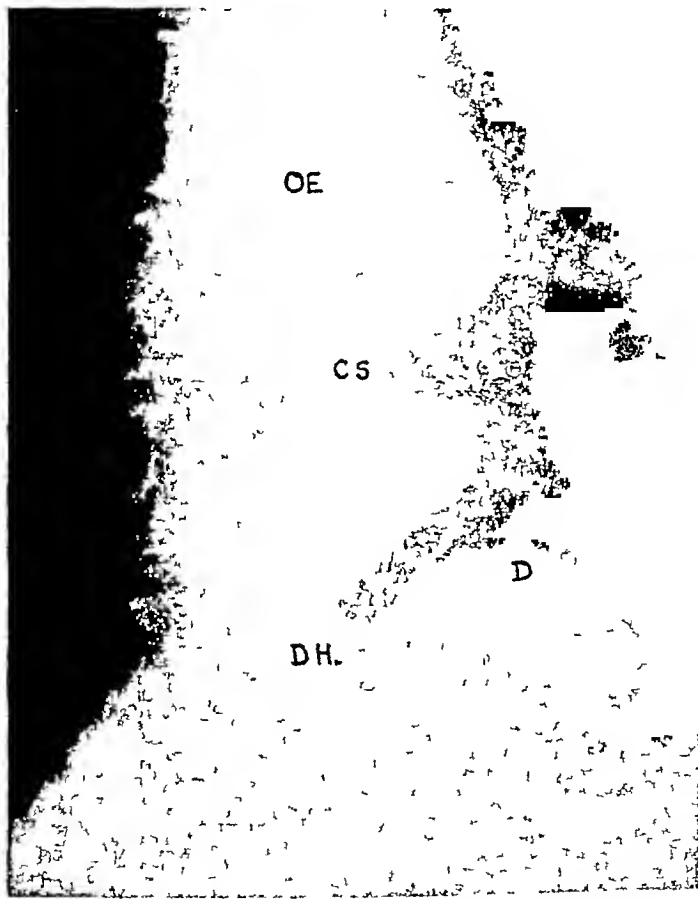


Fig 7A, Case 9. A different view of Case 9, same as shown in Fig 7.

obtain satisfactory dilatation to use graduated Jackson's bougies. Operation was not done in any of our cases. When the ulcer has been healed, the patient should be placed on an ulcer regimen for several months. Infected teeth and diseased tonsils should be treated. If there are any missing teeth, proper dentures should be provided in order that all food may be properly masticated. Patients with oesophageal ulcer should be under careful observation for several months.

Peptic Ulcer of the Oesophagus responds to adequate treatment.

The duodenal tube is of value in the treatment of this disease.

I am grateful to Dr. Malcolm Hall of the X-ray department of the Toronto General Hospital for the interpretation of the X-ray films submitted in this article.

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Symposium on Diabetic Retinitis

(Sponsored by the N Y. Diabetes Association)

Held at the New York Academy of Medicine on the evening of March 16, 1943 Dr George E Anderson of Brooklyn, N Y, Chairman of the Committee on Internal Medicine, Presiding

Dr Anderson This meeting is being held under the auspices of the New York Diabetes Association

The consideration of diabetic retinitis involves not merely the eye. It is more far-reaching in scope, embracing the entire subject of vascular degeneration in the diabetic. The eye-ground presents an excellent vantage point at which to visualize and study the life-cycle of this degeneration from its incipience to its terminal stages.

I am delighted to introduce to you a man of national and international prominence, Dr Sanford R Gifford, Professor of Ophthalmology, Northwestern University Medical School, Chicago, who will present the problem of treatment of diabetic retinitis from the point of view of the ophthalmologist. The medical aspects will subsequently be presented by internists championing somewhat different viewpoints, one, the conservative, favoring meticulous orthodox diabetic control, the other, rather more liberal as to what constitutes ideal control.

Paper by

SANFORD R GIFFORD, M D *

I HAVE failed in my attempt by correspondence to convince Dr Anderson of my inadequacy for this assignment. But the word of mouth is always most convincing and I feel that I am about to succeed in convincing him. Of one thing I am certain. I will take away with me much more than I have brought. The idea of an evening devoted by this distinguished society to diabetic retinopathy struck me as an excellent one and I feel greatly honored in being asked to take part in it.

My reference to inadequacy is no mere polite gesture, since I have never examined a large series of diabetics for statistical purposes as has been done by a number of ophthalmologists, and supremely by Waite and Beetham of the Joslin Clinic, Wagener of the Mayo Clinic, and Hanum of the Rigs Hospital at Copenhagen. It is to these series that we must go for actual facts as to the incidence of various ocular and especially retinal lesions in diabetes. All that I can do is to summarize the pictures which one sees in dia-

betics and to give my impressions as gathered from observing a fair number of diabetics in office and hospital practice. My gleanings from the literature I shall in large part, spare you.

The usual picture of diabetic retinopathy (this name being preferred, for obvious reasons, to retinitis) has been well described by Wagener. The small round hemorrhages are small and round because they are deep in the retina and hence correspond to the deeper end ramifications of the vessels. These and the small discrete white deposits, distributed especially in the central area, constitute the findings typical of diabetic retinopathy. The number and arrangement of these hemorrhages and deposits varies from a few of each scattered through this area to rather large masses of deposits which tend to occupy the macular area itself. Either hemorrhages or deposits may be present alone but most cases show both. The condition is nearly always bilateral. Flame-shaped hemorrhages in the nerve-fibre layer are seen in some cases but are just as common in arteriosclerotic and hypertensive retinopathy alone. In a number of older patients who have developed hypertension a combination of the two conditions exists. Diabetics with retinopathy are, in fact, somewhat more apt to show hypertension than are other diabetics, 52% as opposed to 30% in Hanum's series. It is not true, however, as was formerly supposed, that the retinal changes seen in diabetes depend on hypertension, since many occur in persons with normal blood pressure and most cases show normal kidney function. In Wagener and Wilder's series of 1052 diabetics 11% showed the lesions of ordinary hypertensive-vascular disease while 16.6% showed the characteristic picture seen in diabetes alone. Waite and Beetham, who carefully graded the vessel changes in their cases, found no more sclerosis of the retinal vessels in diabetics with retinopathy than in other diabetics of corresponding age.

When one sees a patient with round hemorrhages and discrete white deposits in the central area without visible changes in the main branches of the retinal arteries, one is justified in considering the picture to be that of diabetic retinopathy, and this tentative diagnosis will nearly always agree with the clinical findings. Emphasis is laid on the discreteness of the white deposits. They are sometimes called "hard" or

*From the Department of Ophthalmology Northwestern University Medical School Chicago

'waxy,' but the idea to be conveyed by these expressions is that their outlines are distinct. Even in the larger masses of white deposits, outlines of the individual deposits can be made out and the outlines of each large mass are clear. Fuzzy or blurred outlines indicate surrounding retinal edema and the presence of edema, especially about the nerve head immediately suggests hypertensive disease. If in addition there is extreme constriction of the retinal arteries, the patient with or without diabetes is usually in the malignant phase of hypertension. If the arteries are not extremely constricted but show marked nicking of the veins and variations in caliber, the patient will usually show a moderate elevation of blood pressure, with in some cases, a history of a cerebral or coronary vascular accident. In other words, absence of edema and of gross changes in the retinal vessels in the presence of retinopathy of the type described is the picture of pure diabetic retinopathy.

I have been discussing the usual form of retinopathy which is seen either in its pure form or in association with lesions due to hypertensive disease in from 10 to 10% of diabetics. The 40% in Waite and Beetham's series of 2002 diabetics was in comparison with 9.7% of 157 controls of corresponding age-groups. For the pure form no relation was found between the incidence of retinopathy and sclerosis of the retinal vessels, hypertension, renal disorders, height of blood sugar, blood calcium, or the use of insulin. Apparently the only factor governing such incidence was the duration of the disease; the incidence of deep hemorrhages reaching 50% in patients who had been known to have diabetes for fifteen years. Age itself may play a part as the incidence of deep hemorrhages in this series increased from 4% in the third to 30% in the seventh decade of life. It is only natural that the increase in life expectancies of diabetics from 14 years before 1911 to 12.5 years in 1940 should produce an increased incidence of retinopathy. Most patients with diabetes now die from arteriosclerosis according to Root and many of these will lose more or less vision from retinopathy before they die. Parenthetically it may be well to quote Hanum's figures on the mortality of diabetics with retinopathy. He found the mortality of male diabetics with retinopathy to be 27 and that of females to be 16 as compared with the norm of diabetics without retinopathy.

There is another type of retinopathy, much less common than that which has been described but important because it nearly always leads to complete or practically complete blindness. This is the condition in which large pre-retinal hemorrhages and hemorrhages into the vitreous occur followed by a growth of new vessels into the veils of connective tissue left by the incomplete absorption of such hemorrhages. This picture known as retinitis proliferans was found in 12% of Hanum's series and 14% of Waite and Beetham's. Most of the patients in these series were over 50 years of age, most showed hypertension and Waite and Beetham dismiss the condition as probably the result of hypertensive disease. They ascribe no

importance to the use of insulin as 29% of their cases had received none. Hanum who has reported his twelve cases in detail, comes to different conclusions. While all of his patients were over 49, and while a number of them showed hypertension and nephrosclerosis, other findings seemed to him of significance. Four of his patients had undergone amputations for gangrene and he quotes a Gray's series, in which all cases developed gangrene. Three of Hanum's patients had definite signs of acromegaly. Most important of all the cases studied as to capillary fragility all showed definitely increased fragility and also low blood ascorbic acid levels. The first hemorrhage in one case occurred when insulin was begun while in another case it followed a very slight trauma. Coagulation time was essentially normal in his cases. Hanum treated a group of these patients with citrin and ascorbic acid. No effect was noted from use of the latter, but citrin brought the capillary fragility to normal in two cases and improved it in another. He thought citrin might have been of value in preventing further hemorrhages in two cases while in a third further hemorrhages occurred in spite of treatment. Of the twenty-four eyes of his twelve patients only two possessed a slight remnant of useful vision.

My own experience leads me to agree with Hanum that there is something about this picture peculiar to diabetes and peculiar to a special group of diabetics. I have seen at least ten such patients within the past five years, such pitiful cases as to remain distinct in memory. Of the twenty eyes of these ten patients only two had useful vision. None of these patients to my knowledge had undergone amputations for gangrene. In contradistinction to the two series just mentioned, mine included several younger persons: a man of thirty, a man of thirty-eight and one of forty-five. All had been receiving insulin. Capillary fragility tests were made on only five of these patients. One was normal while the other four showed definitely increased fragility. Since all but one of these patients were already practically blind treatment for this condition was given in only one case. The picture differs from that of juvenile recurring hemorrhages in that the anterior vitreous remains clear and in the peculiar brush-like vessels which grow out from the retina into the veils which cover the retina and especially the disc. It is not seen in this typical form to my knowledge in hypertensive retinopathy. The blindness results from the fact that these veils of connective tissue cover large areas of the retina and often produce localized detachments which are not amenable to the usual operative treatment. There is no time for further discussion of this picture but to me it forms a very interesting special group of lesions peculiar to diabetes and one deserving more study along the lines suggested by Hanum.

A condition which may have some relation to the picture just described is thrombosis of the retinal veins. I have a very distinct impression that it occurs much more commonly in diabetics than in other

persons, since I have seen at least five such cases within recent years. Two were bilateral and one of these involved the central vein of both eyes. This patient was a man of thirty and the thrombosis was followed by hemorrhages into the vitreous growth of new pre-retinal vessels as were described in the previous group, and glaucoma. Wilder has described marked dilatation of the veins as being common in diabetes and states that these dilatations are often localized suggesting partial thrombosis. He describes the occurrence of vitreous hemorrhages in patients with such veins, resulting in retinitis proliferans.

It was formerly believed that the lesions of diabetic retinopathy could be explained as due to arteriosclerosis. This belief has evidently influenced Joslin and his associates in their discussion of the subject and has led to Root's statement that "The chief cause of premature arteriosclerosis (and, by inference, retinopathy) in diabetes is an excess of fat in the body, diet, or the blood due to lack of control of the diabetes." Recent studies, however, indicate that, although a diseased condition of the vessels must be postulated, this is by no means the same as that seen in ordinary senile arteriosclerosis. In diabetes, most observers agree, it is chiefly the coronary vessels and vessels of the lower extremities which are affected, and to this I would certainly add the retinal vessels. Although cerebral vascular lesions are said to be rare in diabetes we do see paralyses of ocular muscles which can only be explained as being due to small intra-cranial vascular lesions. I am told by Dr. de Takats that the peripheral gangrene of diabetes is due to occlusive endarteritis affecting chiefly the smaller arterioles. This seems to be the case in the ordinary form of retinopathy, except that even smaller vessels are involved. It is the capillaries themselves which must be involved, as the visible vessels are frequently normal to examination. The white deposits are probably best explained as being due to occlusion of the arterial limb of capillary loops. This causes microscopic areas in which the retinal cells become necrotic, since the retinal vessels, especially in the macula, are without anastomoses. Such microscopic areas of necrosis become the seat of lipid and hyaline deposits, which give them their appearance. Some white deposits may also replace deep hemorrhages. Elwyn has made out a good case for involvement of the capillary loops as being the essential factor in the process. He explains both hemorrhages and deposits as due to slowing of the capillary circulation, a condition which he calls peristasis and prestasis resulting in deficient oxygen supply to the tissues. He believes that continued hyperglycemia must be considered responsible for the changes in the vessels. He does not explain, however, why the condition occurs with the same frequency and severity in diabetics with mild or moderately severe diabetes as in cases with severe and uncontrollable hyperglycemia, nor why, as was shown by Leopold's series, the changes seem to occur with the same regularity in patients whose blood sugar is kept under careful control as in other cases.

To explain the special type of retinopathy resulting in retinitis proliferans, and possibly also retinal venous thrombosis, some peculiar condition other than hyperglycemia must surely be invoked. I am able to invoke it, but not to make it appear. Apparently there are no transition forms between ordinary diabetic retinopathy and this condition. Nothing is wrong with the coagulative mechanism of the blood, so far as is known. According to de Takats, peripheral angiospasm is not found in patients with diabetic gangrene, and hence it is probably not present in this type of retinopathy. Piessoni tests might well be made in a series of patients, however. Not enough cases have been tested as to capillary fragility, but if increased fragility is found to be as common in this condition as Hanum found it in his series, this will help greatly in explaining the hemorrhages. It will not, apparently, explain venous thrombosis, and it seems likely, as Wilder implies, that degenerative changes are present in the veins themselves.

This brings us to the subject of treatment, most of which I gladly leave to my successors. It has not been my experience that the usual control of the diabetes by insulin or diet has had much effect on the course of retinopathy. Even when the discovery of retinopathy brings about the first diagnosis of diabetes, the lesions usually progress in spite of medical treatment. They progress slowly in the usual case with long stationary periods. Patients usually retain fairly useful vision in one or both eyes, although reading often becomes impossible. Dr. Anderson's ideas on the optimal type of control seem the best which have been offered and we have been fortunate to have had the matter so clearly presented by him in one of our special journals. Following a report of Friedenwald (read but not published) Puntenney and I did capillary fragility tests on 24 patients with diabetic retinopathy and found 10 with definitely increased fragility. The treatment which he advised with ascorbic acid and Vitamin B complex was carried out in most of these cases but without definite results. This was only to be expected, as the real capillary fragility factor, citrin, was not employed, and Friedenwald's later results, according to a personal communication, were similar. Small doses of citrin were then employed, also without effect. Only recently the Abbott Laboratories have made available a supply of hesperidin, containing citrin in high concentration, with the recommendation that doses of 15 grams per day be tried in such cases. Not enough time has elapsed to give any report on the results.

Dr. Anderson has asked me to discuss the problem of my relations with internists treating diabetes. I have had no problems with internists. My chief problem has been to get the patients to place themselves under the care of good internists who know diabetes and to place the responsibility for care of their general condition upon the internists, instead of running to me all the time to complain about their inability to read.

I was also asked to discuss the preparation of patients for operation especially for cataract extraction. Although the statement is sometimes made that the cataract operation offers no particular complications in diabetes under proper control this does not agree with my experience. I have had plenty of trouble with diabetes especially as regards post-operative hemorrhage. Recurrent small hemorrhages from the iris have occurred with especial frequency and a few larger hemorrhages have occurred spontaneously or following very slight trauma. One patient lost most of the vision in both eyes due to hemorrhage following glaucoma operations an exceedingly rare occurrence. It has become a routine to run blood sugar as well as urine sugar tests pre-operatively on all cataract patients, and this has saved some unpleasant surprises. I try to allow enough time before operation so that good control may be established and agree with Wilder that this had best be done with as little insulin as possible or, if possible, with no insulin at all. I think his advice to omit insulin if possible just before and immediately after operation is sound. Capillary fragility and blood ascorbic acid will be determined in the future in all operative patients known to have diabetes. All cataract patients now receive 100 mg. of ascorbic acid daily for a week before and after operation and when enough eltrin is available, this will be given to those showing increased capillary fragility.

In conclusion, I must agree with Anderson that more important than treatment is the prevention of diabetic retinopathy. Perhaps the high fat, low carbohydrate diet used by many diabetics has been responsible for many vascular changes and measures designed to limit the amount of fat in the blood, either from the diet or the tissues themselves will help to prevent them. There seems a good possibility that some of the severe degrees of retinitis proliferans can be prevented, or if detected early, prevented from producing complete loss of vision. This would require that capillary fragility, and probably also blood ascorbic acid levels be determined in all diabetics and that all patients with abnormal findings should be submitted to careful control for the balance of their lives of these factors. It would seem that in such cases special care to avoid insulin reactions should be taken and that the amount of insulin should be kept to the minimum compatible with adequate control.

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Dr Anderson Thank you, Dr Glifford Before we have a discussion of this paper, we shall hear from the

conservative side of the medical problem represented by Dr Louis Lauman of the Presbyterian Hospital

Paper by

LOUIS LAUMAN, M.D.*

AN idealistic viewpoint with regard to the prevention of diabetic retinitis after a long experience with the underlying disease, is obviously, tempered by the difficulties encountered in maintaining continuous control. It would appear to the speaker at least that the end warrants the means. At any rate it seems worth while to give continuous control a fair trial over an extended period.

The following data concerning diabetic retinitis are worthy of comment.

1. A number of observers, including ophthalmologists believe that arteriosclerosis, secondary to diabetes is the chief cause of retinitis in the diabetic. All agree that hypertension is an aggravating influence. Some think that diabetes alone can produce retinitis.

2. The incidence is greatest in mild, long-standing diabetics after fifty.

3. Some state that continuous careful control of the disease does not prevent the eye changes. Since there is no agreement among diabetic specialists as to what constitutes efficient regulation these statements are not conclusive. If continued sugar freedom and normal blood sugars are an indication of efficient control then few if any of the cases cited meet this requirement. In evaluating the effect of treatment the influence of the preceding period of neglect or non-treatment cannot be ignored.

4. A twenty-year study of two comparable groups of adult diabetics, free of retinal changes the one meticulously regulated the other less carefully controlled might furnish the answer.

5. At the present time, we consider a diabetic patient at the outset of the disease a normal person with an insufficient supply of insulin therefore a well balanced adequate diet and the requisite amount of insulin should maintain a normal state of health and prevent the dire complications of the disease. The other serious complication is due to arteriosclerosis of the peripheral arteries with interference of circulation in the feet and ultimately gangrene. It is significant that retinitis and retinal hemorrhages are an almost invariable accompaniment of the foot condition and both are probably preventable.

The usual cause of poor control of diabetes is lack of restraint and co-operation on the part of the patient.

At times too casual advice by the physician leads to the same result. Such remarks as "cut down your carbohydrate" or "take a small dose of insulin when you show sugar" invite carelessness and tend to minimize the importance of persistent careful regulation. In many older diabetics the absence of sugar from the urine is not a safe guide, for these patients may retain

*Presbyterian Hospital, New York.

sugar in the blood to the extent of 300 mg per cent without glycosuria

The periodic examination of the urine after middle age is to be encouraged so that delayed recognition of the disease may be avoided. As previously stated, there is no agreement among physicians as to what constitutes efficient regulation. While some, such as Boyd of Iowa insist on normal blood sugars throughout, others, including one of our local colleagues, permit the passage of large quantities of sugar in the urine. This is naturally confusing to the general practitioner and it is therefore encouraging that the American Diabetes Association has appointed a committee to study this important question of adequate control. Dr Mosenthal may have a word to say on this subject.

The ideal in therapy is restoration to normal, and this goal is approachable in many cases of diabetes. In some, owing to occupation or to unusual lability of glycogen mobilization, this is difficult or impossible to attain but with the newer depot insulins and the shifting of the carbohydrate from one meal to another, even these difficulties may be lessened or overcome. Dr Boyd and associates of the State University of Iowa in a report based on the records of 250 diabetic children conclude that "in general, the freedom from degenerative changes has paralleled the excellence and continuity of diabetic control." O'Brien and Allen, also of Iowa, encountered 23 cases of diabetic retinopathy in a survey of 555 diabetic patients under 31 years of age. What is more significant is the fact that in six cases of retinopathy the changes were transitory. They were observed after six to twelve months of poor control and disappeared in one to two months after strict control was instituted.

It seems good practice to warn the diabetic patient at the outset of the dangers of poor control. In co-operative patients one rarely sees these developments.

The much discussed etiological relationship of increased blood fats and cholesterol to arteriosclerosis may also be concerned with retinitis. One reason for elevated blood lipids in diabetes is the inability of the body to obtain the required energy from the oxidation of CHO. It therefore mobilizes fat and this is transported to the liver via the blood stream before it is utilized. Here again careful regulation prevents this abnormal physiology.

Besides retinitis, cataract is more common among diabetic patients. Perhaps enlightenment of the public with regard to the dangers of obesity, a forerunner of diabetes and hypertension, is the best way to prevent these eye complications. The knowledge of food-values which is being disseminated by the Red Cross and other agencies will probably accomplish much to prevent obesity.

While strict adherence to diet and insulin dosage is the responsibility of the physician, this treatment is rather a simple matter if proper co-operation is obtained from the patient. Briefly, all adult diabetic diets should contain at least 70 grams of protein, two glasses of milk, vegetables, and fruits. The deficiency

in Vitamin C, referred to by Dr Gifford, can easily be remedied by a liberal amount of grapefruit, orange, strawberries, and canteloups, which are the fruits richest in Vitamin C. The total food requirement depends on whether the patient is underweight, normal or overweight. The calculation of food values becomes a simple matter if one of the many compilations is used. A very simple and inexpensive one is that arranged by Anna de Planter Bowes of Philadelphia. There is no reason why a diabetic should not be on a diet well balanced in every respect.

Most patients can be controlled with protamine zinc insulin alone or combined with a separate dose of regular insulin. Globin insulin, which will soon be on the market, is preferable to protamine zinc insulin in certain cases because its action is more rapid but yet sustained. Ambulatory cases returning monthly or every two months, bring small samples of urine passed before breakfast, lunch, dinner and bedtime. If these are all negative, a blood sugar is taken to detect a high renal threshold. In an ambulatory clinic of the Presbyterian Hospital 60% of the last three hundred blood sugars were normal.

Prolonged clinical experience warrants the view that diabetic retinitis is a preventable condition. Let us therefore adopt a more aggressive attitude and hope that this will lessen its incidence or eliminate this tragic complication. We are in full agreement with Dr Gifford as to the advisability of pre- and post-operative regulation of the diabetic eye patient. Preliminary rest in bed and sedatives tend to lower blood pressure and lessen the danger of post-operative hemorrhage.

Dr Anderson: Thank you, Dr Bauman. We shall now hear from a representative of the more liberal side of the medical problem, Dr Harry G. Jacobi of the Lenox Hill Hospital.

Paper by

HARRY G. JACOBI, M.D.

IN discussing this subject, one must admit the rather disappointing fact that up to the present time, our knowledge of this lesion appears to be based upon its recognition combined with whatever information can be obtained from statistical deductions. Various investigative attempts have been made to associate the occurrence of retinitis in the diabetic with some particular element or phase of the diabetes or its complications. While these investigations have revealed some very interesting and instructive facts, they have been rather inconclusive from the etiological viewpoint, for they have shown that this lesion may be found to occur just as frequently in those diabetics who have been subjected to the most rigid control by diet and insulin, as in those who have had improper or inadequate management. Nor does the severity or mildness of the diabetes have any precipitating or inhibiting effect, for the lesion apparently occurs just as frequently in the mild diabetic as in the severe case.

Furthermore, one cannot help repeatedly becoming

impressed in these cases with the observation that particularly in the early stages these excursions appear to show a tendency to a much slower progression when the patient is maintained on a more liberal carbohydrate intake.

Such a state of affairs in itself however would hardly justify the conclusion that all careful regulation of the diabetic patient with retinitis is useless and that it would be just as well to let such patients enjoy complete freedom from supervision. Any such conclusions are indeed unwarranted and pericious.

We are also becoming convinced of the fact that these retinal hemorrhages are sometimes not due solely to the retinal sclerosis nor are they necessarily the accompaniment of a hypertension. There indeed seems to be some indication that such additional factors as increased permeability of the retinal vessels or a generalized increase in the capillary fragility may also be involved in this process. This has led to the suggestion that retinitis may even be the result of a deficiency state possibly in the C vitamin together with perhaps some factors in the P complex.

Let us then examine the facts which would justify a liberal viewpoint in the management of the diabetic in these cases of retinitis. In support of the more liberal respect we find that considerable evidence has accumulated which tends to show that under certain conditions increased carbohydrate ingestion by diabetes has resulted in increased carbohydrate retention, increased glycogen deposition, and more effective carbohydrate utilization. The fact that such increased carbohydrate intake is followed by an increase in the glucose level in the blood stream is not necessarily of itself indicative of a harmful condition except when such increase is accompanied by marked glycosuria and polyuria. Such urinary effects are of course, distinctly harmful because of the disturbance in the electrolyte balance of the body which is the inevitable result of such a condition of diabetes. Glycosuria to any extensive degree therefore must be avoided. The dread however with which the question of hyperglycemia without glycosuria is sometimes approached appears to be based on a lack of clear-cut appreciation of all the factors involved and continues to persist in spite of the repeated assertions by many observers that the hyperglycemia in itself is not necessarily an abnormal or detrimental state but may be constructive and perfectly physiological a fact which has been emphasized by Mosenthal. Furthermore, it has been generally conceded that as the individual grows older, such increased blood sugar levels are apt to be present and may very well be a necessary stimulant to maximum insulin production and carbohydrate utilization and also the very means of insuring a more adequate storage of glycogen in the liver. We must also remember that by the same line of reasoning, just what constitutes a normal blood sugar for a diabetic individual, especially an arteriosclerotic diabetic, cannot necessarily be based on the average fasting blood sugar findings in the healthy young individual. Text-book standards are often untenable especially since in

the arteriosclerotic patient such values often represent a relative if not absolute hypoglycemia.

As in all controversial issues, there have been two distinct schools of thought on the subject each advocating its particular view point with extreme vigor. One is represented by the extreme rigid standards set forth by the Allen school, modified by Joslin and his associates and the other consisting of advocates favoring a pronounced swing in the opposite direction. Just how far such radical view points may wander is illustrated by the reports of Tolstoi and Weber, who have maintained that the occurrence of large quantities of sugar in the urine, especially in diabetics treated with Protamine Zinc Insulin is of no consequence or concern, provided there is a liberal carbohydrate intake. Perhaps both viewpoints are faulty and somewhere in between these two lies the course most to be desired when treating the diabetic patient with retinitis. It seems likely that too rigid restriction may be just as bad as excessive laxity.

In my opinion the more liberal view-point seems to have more definite clinical support, for there is no doubt that especially since the introduction of Protamine Zinc Insulin, we have modified our concept of what constitutes the ideal theoretical balance for the diabetic. There has been an increasing tendency to allow more liberal carbohydrate intake and to accept without concern a rather marked increase in the level of the circulating blood sugar provided the glycosuria is mild inconstant border-line or absent. The presence of mild glycosuria is frequently found to be even desirable in the elderly or in the arteriosclerotic diabetic, and it is often spoken of as a safety measure to guard against insulin shock. High blood sugar is perhaps the lesser of two evils in an individual with fragile blood vessels—especially when such vessels are found in the eye grounds. I wish to emphasize again however, at this point that the treatment of the diabetes itself in these cases of retinitis or of peripheral vascular disease in general, is only one of several factors which must be taken into account. Before discussing all of these factors however, it is important to make a few additional qualifying remarks about the so-called liberal attitude in the treatment of these diabetic cases.

It must be stressed first of all that the time element is an important consideration in this as in any regimen whether liberal or conservative. Moderate restriction over a limited period of time may be quite different in its effect from the continuation of such measures over a long or an indefinite period. Increased carbohydrate allowance is especially beneficial when administered to cases which had previously been under very rigid control but this is true only if the increased carbohydrate is carried to the point where it does not cause marked glycosuria with resulting dehydration and dessication of the tissues. Such unfavorable reactions cause loss of electrolytes and proteins, and are distinctly harmful. The mere existence of a moderate degree of hyperglycemia is of itself

however, not only harmless, but has been found to be definitely beneficial, since in many of these patients such hyperglycemia seems to facilitate the body's use of glucose, particularly by the peripheral tissues.

In regard to the hyperglycemia in these diabetics, some useful information may also be obtained from the striking similarity between these diabetic arteriosclerotics and the non-diabetic group, for even in the non-diabetic arteriosclerotic group one frequently observes the tendency to existence of a high blood sugar without any spill-over into the urine. This is so common that it may almost be considered as physiological. In such cases of arteriosclerosis with high blood sugar careful studies of the respiratory quotient shows that these individuals burn or utilize sugar normally even in the presence of the hyperglycemia.

If the same non-diabetic arteriosclerotic be subjected to rigid control of his diet in an attempt to bring his blood sugar down to the so-called normal level, he does not react very well to the regimen. Often he is transformed into a clinically sick man, by such measures. Why then should one attempt such drastic reduction in the diabetic with arteriosclerosis? Any reduction in the accustomed level of the circulating blood sugar of the diabetic with arteriosclerosis actually produces a relative hypoglycemia, even though the blood sugar level is far above the so-called critical hypoglycemic level. This may be far more damaging than an absolute hypoglycemia in the ordinary diabetic. In the absence of glycosuria, there certainly can be no valid reason for the sudden correction with its consequent disturbance as a result of the decreased level of the blood sugar in these cases. Such hyperglycemia per se has never been shown to result in increased tissue breakdown, and even with induced hyperglycemia in the experimental animal normal tissue growth and repair usually take place.

A liberal carbohydrate intake, of course, must automatically preclude a high fat content in the diet. Recently there seems to have developed a greater unanimity of opinion in favor of the maintenance of a low fat metabolism especially as regards its relation to improved carbohydrate utilization. When considered with particular reference to the development of retinitis, this rationale seems to derive some authentic support from the observation that very often when such restriction of fat has not been practical definite disturbances in the fat metabolism seem to precede the onset of the ocular symptoms. On the other hand with the relatively higher carbohydrate low fat regimen now in use, such lesions as lipaemia retinalis are practically disappearing from clinical practice.

What is even more important, in regard to the inter-relationship between fats and carbohydrates in the metabolism of the diabetic, are the very interesting and rather extensive observations which have been made by such investigators as Soskin, Mirsky, Stadie, and others. These observers have definitely shown that the stimulus for increased fatty acid oxidation with the consequent increased acetone-body formation occurs in the liver as a direct result of the liver's di-

minished glycogen content, inevitably resulting when there is too rigid restriction in the carbohydrate intake. When, however, glycogen is present in abundance or at least in ample amount in this organ, there takes place the complete mobilization of certain enzymes which are able to act equally on glycogen or fats, but which seem to have a preferential affinity for the glycogen. When as the result of too rigid restriction of carbohydrate or partial starvation, glycogen becomes depleted from the liver, these same enzymes will act on the fats with a resultant acceleration of the rate of acetone-body formation. This has been called obligatory fat metabolism and takes place only because of a lack of available carbohydrate in sufficient abundance.

Increased fat intake also leads to pathological infiltrations in the vascular system. Thus in various degenerative processes in the body as well as in vascular lesions, many investigators have reported finding increased amounts of cholesterol. Regarding the arteriosclerosis itself, the theory is again becoming popular (as advanced originally by Aschof) that this process precedes calcium deposition. The deposition of calcium as a part of the arteriosclerotic pathological process is quite well established and it seems that the elastic tissue of the vessel walls is particularly prone to such early calcification. The theory of there being a pathological relationship between abnormal depositions of cholesterol and lipoids in the vascular system and the overfeeding of fat seems to be gaining ground. Overfeeding is not the only factor, however, producing such deposition of fat in vessels nor is hypercholesterolemia a common finding in these patients.

Those who have studied this perplexing problem of vascular disease in the diabetic have been impressed by the fact that something seems to happen to the blood vessels of these individuals after their diabetes has existed for a period of ten years or longer. Most of the vessels including those of the retina become in some way vulnerable. The vulnerability of the retinal vessels is obviously better appreciated than it is in most other sites, since these vessels are so accessible to direct visual examination, because they are so much smaller than other peripheral vessels subjected to study, and also because relatively slight damage can be so far-reaching in its effects. Just what they are vulnerable to has interested us for a long time. Also whether certain routines in the management of the diabetes may or may not be responsible for hastening or even initiating this so-called vulnerability has been a pertinent problem.

I have often wondered, however, whether we are really on the right track, in trying to find the answer to diabetic retinitis by assuming that it is related entirely to some feature in the therapeutic management of the diabetes alone. In such an assumption may we not really have overlooked some equally or even more important factors? Isn't it quite possible that the answer to the problem of treatment is dependent not entirely on the handling of the diabetes itself, but is

related to something additional which affects these individuals, and that the diabetes and the manner of its management are merely contributory to the production of the lesion by rendering blood vessels more susceptible to such factors as infections or other toxic agents?

The lesion of retinitis, having once been recognized as being present, the next important step, of course, is to determine what can be done to bring about improvement. Just as in other cases of vascular disease complicating diabetes, the treatment in these patients with retinitis must be directed along certain definite lines. Our attempts have been divided into (1) The management of the diabetes (2) Search for the existence of any focus of infection and its immediate eradication (3) In our hands the effective improvement in the electrolyte balance of the blood plasma by means of daily intravenous therapy with hypertonic solutions of chlorides or iodides, has proven of value even though this treatment has been on an empiric basis (4) Administration of vitamins, principally C and the B complex

Let me permit that I believe that undue emphasis on any one of these factors such as, for example, the control of the diabetes alone will not solve the problem satisfactorily and that such a narrow approach has probably accounted for some of the disappointing results that are all too frequently obtained in this condition.

I wish to take up briefly the question of the intravenous therapy previously mentioned. The role of such substances as iodine in the dissolution of pathological processes has long been championed and has had rather ample clinical substantiation. We have found that many diabetics with vascular disease show a rather definitely favorable response to the intravenous administration of a hypertonic solution of either sodium iodide or sodium chloride. Aside from the clinical improvement noted, the careful follow-up of the blood cholesterol levels during the course of this therapy shows that some change is taking place. After several intravenous treatments with the chloride or iodide solution, a sharp rise in the blood cholesterol is invariably noted. This is followed by a subsequent fall in the blood cholesterol to the pretreatment level as the injections are continued. Such response is not obtained, however, on the oral administration of the salts. The marked improvement observed in these cases is almost analogous to that seen in diabetic acidosis, in which the symptoms of dehydration clear up only after the administration of the required amount of chlorides.

Of the four factors previously mentioned, the management of the diabetes seems to be the principal problem in our discussion this evening, and as I have already mentioned my own observations and experiences have influenced me to favor the so-called liberal point of view. Perhaps a clearer and more practical understanding of this attitude might best be obtained by the actual presentation of a few typical

cases which illustrate all of the above-mentioned factors.

Let us take the case of Mrs. C. F., a 65 year-old white female, who had been aware of her diabetes for 9 years before the onset of her retinitis. She had never taken any insulin nor had she followed any dietary restrictions. Her eye symptoms began about 6 months before admission to the hospital, when she started to complain about blurring of vision. She consulted a local physician, primarily for the visual disturbance, and it was at that time that she also learned of the presence of a hypertension. Hospital admission was recommended for the more careful study of her visual disturbance. At the time she had a fasting blood sugar of 167 mg per 100 cc. of blood, and only a mild glycosuria. Her blood pressure was 180/80, and blood cholesterol was 302 mg. She presented a typical picture of diabetic retinitis with evidence of old and recent hemorrhages in both eyes. Her diabetes was very easily controlled by a diet of P 80, F 75, and C 150. Her retinitis seemed to progress unfavorably while under our observation in spite of the fact that she was maintained in excellent sugar control without the use of any insulin. A careful search was made to rule out possible foci of infection, and it was found that the patient had apical abscesses involving four of her teeth. These were promptly removed, and the patient remained under our observation. Subjectively at the end of about ten days after the removal of these foci, she began to report improvement in her vision. About three weeks later, a check-up of her eye-grounds revealed a definite improvement in the fundi with less retinal edema, and no more fresh hemorrhages were noted. The patient admitted that her vision had improved, and she was discharged. About 6 months later this patient returned to our follow-up clinic. She was still under fairly good control of her diabetes by diet alone. Her systolic pressure was much higher than when she left the hospital. Her vision, however, had steadily improved.

Here is an instance of a mild diabetic who had not been on insulin or even dietary control. She had developed her retinitis and following this a period of strict management of her diabetes had had no influence whatsoever in arresting the progress of her lesion. The removal of 4 infected teeth, however, had a strikingly beneficial effect on the retinitis. This improvement continued in spite of the fact that her hypertension had even increased after discharge from the hospital.

The next case is that of a male, A. R., 49 years' old who was a known diabetic of 8 years' standing. He applied for admission to the hospital on account of pains and swelling in his joints, particularly his ankles and those of his hands, which had set in one year previously. His diabetes had been fairly well controlled during this time. He had been on a diet of P 80, F 90, C 180 with 20 units of Protamine Zinc Insulin. His fasting blood sugar on this regimen was 154 mg. He also complained of impaired vision in the

right eye, and in spite of the excellent control of the diabetes, both the joint pains and the visual disturbance became worse. The X-ray findings of the joints together with the other laboratory examinations such as increased sedimentation rate, etc., convinced us that we were dealing with a rheumatoid arthritis. We were unable to find any possible focus of infection. Treatment was instituted consisting of intravenous injections of iodides and salicylates daily for three weeks. A more liberal carbohydrate diet was allowed, up to 250 Gm of carbohydrates, using, however, the same amount of insulin. His fasting blood sugar had increased only moderately to 164 mg and with only slight glycosuria as a result of this. After a period of about 2 weeks on this routine a definite improvement was noted in the arthritis, and also in the eye symptoms. Here is a case of the moderate diabetic, who developed both a rheumatoid arthritis, and a retinitis. The lesions did not show any improvement on the very rigid dietary management, but changed after liberalization. Just what part the intravenous administration of the iodides and salicylates played, is unknown but is of extreme interest especially to the ophthalmologists who in general lean toward the use of iodides in this condition.

The last case I should like to present briefly is a male, E. D., aged 61 years, whose diabetes dates back to 28 years ago, when he was rejected for life insurance. Eight years ago he had been placed on a rigid diet with 20 units of regular insulin in the morning, and 20 units at night. His urinary output was as high as 4% sugar at times. Three years previous to admission he had been placed on Protamine Zinc Insulin 40 units, with a diet approximating P 60, F 70, C 150. He presented a diabetic retinitis together with an ulceration of the right foot. On admission to the hospital his blood sugar was 200 mg and CO_2 combining power was 51.9 volumes per cent. Cholesterol was 250 mg. He was allowed a more liberal carbohydrate intake up to 250 Gm with protamine insulin maintained at the same level of 40 units. He was also given from one to three grams of sodium iodide, intravenously, dissolved in 250 cc of saline. Under this regimen the ulceration of the foot healed completely and simultaneously the eye-ground changes improved. A very interesting variation took place in the total cholesterol during the intravenous therapy. It rose to as high as 400 mgs and then dropped back to about the original level. At the time of his discharge this patient was able to take P 70, F 80, C 175, with Protamine Zinc Insulin 30 units, and showed at that time a fasting blood sugar of only 140 mg on this regimen.

I have merely cited these few cases to illustrate more clearly the problem under discussion. There seems to be no relation between the severity of the diabetes or the strictness of the diabetic management and the progression of the eye lesions. Such increased progression in the retinitis has been observed in cases of mild diabetes in which the carbohydrate metabolism has apparently been maintained under excellent con-

trol, while in other cases in which the management has been definitely poor from the diabetic point of view, the eye lesions have exhibited no progression. Some of our patients apparently showed the existence of retinitis without any other demonstrable signs of vascular disease elsewhere in the body, and such observation must mean that the diabetes does something either to injure the finer arterioles or venules of the retina or to render them more susceptible to the injurious action of other agents. In my opinion, the whole problem seems intimately connected not only with carbohydrate and fat metabolism, but also with salt metabolism. The exact method or processes involved would certainly require too lengthy a discussion for this evening. Let it suffice to say that high blood sugar per se without glycosuria has never been shown to speed the evolution of the retinitis but seems actually to be beneficial. If this is true, one should not attempt to reduce such blood sugar either by stringent dietary measures or by the heroic use of insulin. Anderson has suggested that the function of insulin in these patients is to maintain a blood sugar just below or near the spilling-over point. Heroic insulin dosage has probably been responsible for some of the hemorrhages in these patients—especially after cataract extraction.

Limited periods of increased carbohydrate allowance without a corresponding increase in the insulin dosage has had a definite and beneficial effect on these cases of vascular disease in the diabetic. If carbohydrate metabolism is to be pushed, the diet must needs be liberal in carbohydrate at the expense of fat restriction. In addition, Anderson has emphasized that the diet should, however, be sufficiently adequate from a caloric standpoint to prevent weight-loss, for a restricted caloric intake only leads to undesirable obligatory fat metabolism. I am convinced, however, that additional investigative work is necessary before jumping at conclusions. Adherence to the orthodox strict control of the diabetic, has certainly not offered the solution. The solution is not mere liberalizing of carbohydrate intake but can be reached only by discovering and restudying the other possible factors such as I have suggested as being involved in the process.

Dr. Anderson: Thank you, Dr. Jacoby. I shall now ask Dr. Conrad Berens of New York to open the discussion of Dr. Gifford's paper.

Paper by
CONRAD BERENS, M.D.

IT is a pleasure to discuss a paper by a man whose modesty is only surpassed by his knowledge of the subject.

Hemorrhages seen in diabetes uncomplicated by hypertension are somewhat characteristic, but in my experience there is no one ophthalmoscopic sign that permits the diagnosis of diabetic retinopathy with absolute certainty although the macular and paramacular changes are often most suggestive. It is evi-

dent, as shown by the studies of Waite and Beetham that hypertension is apparently not the principal cause of hemorrhages in the retina, as 62 per cent of their patients with diabetes who had deep retinal hemorrhages had a diastolic blood pressure under 90 mm of mercury. In a group of fifty diabetic patients who were operated upon for cataract and studied in association with Dr. M. Smith at the New York Eye and Ear Infirmary, twenty had diabetic retinopathy. In this group of twenty patients who averaged sixty-three years of age, the blood pressure averaged 115/64. Of the thirty patients without diabetic retinopathy the blood pressure average 163/92. Eleven of the fifty patients had hemorrhages following cataract extraction and their blood pressure averaged 117/82, post-operatively. From these figures it would be difficult to implicate hypertension as the cause of the retinal hemorrhages.

I am particularly interested in Dr. Gifford's differentiation of the picture of diabetic retinopathy and the retinopathy of malignant hypertension. Oppenheimer's pathological studies clearly indicate the difference in the kidney picture in benign hypertension as compared with that in malignant hypertension (*Arch. Int. Med.*, 16:401, 1931). In Fishberg's and Oppenheimer's ten cases of essential hypertension with malignant hypertensive retinopathy in which the patients came to necropsy, necrosis of the renal arterioles was present. On the other hand necrosis of the renal arterioles was absent in eleven cases of essential hypertension without malignant hypertensive retinopathy that were studied at necropsy. It would be of great interest and importance to compare the kidney pathology in diabetes without retinopathy with the kidney pathology in diabetes with retinopathy.

The higher percentage of retinal hemorrhages in the later stages of diabetes is generally conceded. If the blood pressure is low in many of these patients with retinal hemorrhages as compared with those with no hemorrhages, hypertension is probably not the important factor in the production of the retinopathy. It is my belief that some toxins either metabolic or bacterial may be factors in producing the retinopathy, possibly in association with the prolonged presence of sugar. Moreover consideration should be given to toxins from chronic infection as factors which may increase the permeability of the capillaries, the degeneration of which may account for the round deep hemorrhages. Some of these same vascular changes are present in patients with advanced nephritis but are even more destructive in the retinas of diabetic patients. The larger more superficial hemorrhages are usually the result of thrombosis of the retinal veins. Sclerosis and thrombosis of the veins may be present in advanced hypertension and nephritis and commonly in sclerosis without hypertension but these changes are more marked in the retinas of diabetics.

It is pointed out by Dr. Gifford that the arterio-sclerotic factor is most important. At the time the eyes of diabetics are seen in the laboratory practically all the retinal and choroidal vessels (veins and

arteries) show a fairly advanced degree of sclerosis. Cohen has found early arterial changes in pathological sections of the retina which were not demonstrable clinically.

I am inclined to agree with Dr. Gifford that retinitis proliferans is not merely an hypertensionic basis whether seen in diabetics or non-diabetics. Dr. Gifford's suggestion of thrombosis as an important factor is one which I believe should be given careful consideration especially in view of the pathologic findings in diabetic retinitis. I would be interested in knowing whether many of our diabetic patients with retinitis proliferans and thrombosis of the retinal veins show evidence of chronic phlebitis in the jugular veins or veins of the legs.

It would fit my hypothesis to consider capillaritis as a cause of some of these lesions of the retina. We have studied the capillary permeability of our diabetics following Friedenwald's suggestion that ascorbic acid and Vitamin B complex might be of some benefit in these cases but could see no apparent benefit from this treatment. I have had no experience with the use of citrin.

My ideas are in accord with Dr. Gifford's explanation of the pathology of the waxy deposits in the retina and I agree that Liwy's conclusion that the sugar is the cause of the deep retinal pathology is probably incorrect.

Dr. Gifford's statements that the retinal changes in diabetes are not controlled by insulin and that this preparation seems to have little effect on the course of the retinopathy are in accord with my experience. When insulin was first administered I thought it even had a deleterious effect and still believe that insufficient attention is given to diet in many cases. Moreover, when hemorrhages have developed, insulin should be used with care and be carefully controlled.

My experience in treating diabetic retinopathy with any of the suggested forms of therapy has been as unsatisfactory as Dr. Gifford's. The retinopathy usually seems to progress even though the sugar in the blood and urine is controlled. I am aware of the fact that some good results are reported from controlling diabetes. Injections of retina, which was suggested as a cure, were administered to some of our patients but without apparent success in preventing the progress of the retinopathy.

Dr. Gifford spoke of patients with inability to read. This brings up the question of a central scotoma (sometimes found in diabetics) which interferes with their reading ability. A patient was seen recently whose blood sugar was 225 mg and who had a central scotoma in each eye. Vitamin B, which is reported to have been beneficial in similar cases, was administered. Some circulating toxins may be responsible for this lesion, the peripheral neuritis and ocular muscle paralysis seen in diabetics.

Our experience with post-operative hemorrhage in fifty cataract operations performed on diabetic patients is as follows. Post-operative intra-ocular

hemorrhage was observed in eleven patients whose average age was sixty-two years, and five were treated with and six without insulin. Twenty patients averaging sixty-four years of age, who had diabetic retinopathy, were operated upon. Three of these patients had post-operative hemorrhage while seventeen did not. Nineteen were treated with insulin and one was not. Apparently neither the diabetic retinopathy nor the use of insulin seemed to influence the incidence of post-operative, intra-ocular hemorrhage in these diabetics.

The attending physician is asked to control the diabetes pre- and post-operatively, and I am still not sure whether it is necessary to omit insulin just before and immediately following extraction of cataracts although I prefer this routine. I have not hesitated to continue to have it administered when the diabetes could not be controlled sufficiently.

The work of Parker Heath (Arch Ophth, 10 342 1935) seems to lend some support to the suggestions that the metabolism of fats should be considered more seriously than it often has been in the treatment of diabetic retinopathy. It has been shown by Sugeta (1923) that disturbance of the lipid balance of the blood can produce lesions in the retina similar to those of diabetic retinopathy if this tissue is diseased.

Dr Gifford has avoided the subject of chronic infection in patients with diabetic retinopathy, but it is my impression that we should give careful consideration to their conservative elimination in addition to the excellent suggestions that Dr Gifford has made in his constructive paper for more careful study and treatment.

Dr Anderson: Thank you, Dr Berens. The discussion of the medical aspects will now be opened by Dr Herman O Mosenthal of New York.

DISCUSSION

DR HERMAN O MOSENTHAL: Since 1914, I have been very much interested in the subject of diabetic retinopathy. In the pre-insulin period, for four years at the Johns Hopkins Hospital, we examined a considerable number of diabetics and, by and large, did not find retinal lesions in any diabetic patient whose condition was not complicated by either albuminuria or hypertension. According to the best of my belief, this was the prevalent opinion at that time and persisted until the reports of the Joslin group and that of the Mayo Clinic were publicized. Even now, it seems to me that the serious retinal lesions found in diabetics are not as common as we have been led to believe, and are largely the result of constitutional changes which occur independently of the diabetes. I am making these statements as a general practitioner interested in diabetes and not as an eye specialist.

The most prevalent retinal lesions in diabetes, I believe, are supposed to be hemorrhagic ones. These impairments, some of my ophthalmologic colleagues have told me, were really the characteristic findings in diabetics. As we have heard here tonight, the retinal changes in diabetics occur mostly in older persons.

The population as a whole, thanks to control of infectious diseases, and diabetics, owing to the use of insulin, are attaining greater age than they ever did before, and it may very well be that this aging of the diabetic population may be a factor in this situation.

Retinal hemorrhages are found in some persons who are perfectly normal in every other respect. The same may be said to be true of more extensive retinopathies, so that we should be extremely careful in putting the blame on the diabetes in producing such lesions.

Recently one of my patients with severe recurring and advanced retinal pathology was diagnosed on inspection by an eminent ophthalmologist as showing typical diabetic retinitis. This was hailed by his medical colleagues as a very astute diagnosis. It is true that the patient had a mild diabetes, but the fact remains that the patient had distinct albuminuria, some impairment of renal function and a systolic blood pressure over 200 at that time. It would surely be a question in this case, as in many others, whether the diabetes or the nephritic state were to be regarded as the cause of the retinitis.

With advancing years and arteriosclerosis doubtlessly many, if not most, instances of diabetes in persons over fifty (in which age-group diabetes is most prevalent) are the result of arteriosclerosis which has impaired the pancreas as well as other organs throughout the body. Such a diffuse arteriosclerosis could, of course, affect the eye-grounds and be responsible for a good deal of retinitis on a constitutional vascular basis rather than on the diabetic basis.

This idea of diabetes being part of a diffuse vascular disease is illustrated in another direction. The finding of intracapillary glomerulosclerosis in diabetes has become a routine matter on the part of some pathologists, whereas Kimmelstiel and Wilson in their original paper said that this lesion was only found in three to four per cent of diabetic persons. Arthur Allen more recently says that it exists in seventy per cent of cases and is the most diagnostic histologic characteristic of diabetes. On the other hand, some authors apparently find this lesion also present in many cases of chronic nephritis which are not afflicted with diabetes. Under the circumstances, it is difficult to make up one's mind what part of the picture is due to diabetes and what part is due to nephritis or a primary vascular disease. The same view may be held in regard to that retinitis which has been described as characteristic of diabetes.

The point I am trying to make is that vascular changes which commonly occur in diabetes may, in the first place, be unrelated to the diabetes per se, and in the second place, may occur in non-diabetic individuals. I should think the same reasoning might be applied to the retinal lesions that we have been discussing. A diffuse vascular disease would explain the whole situation without considering the diabetes as a primary cause for the arterial involvement but rather as an effect of the vascular disease. In this category

the eyes, the kidneys, and other organs might very well be included

The various methods of treating diabetes all have their advocates and each one of them is supposed to preserve the integrity of the body and to prevent such complications as retinitis better than any other. The various diets and various standards of control that have been proposed are legion and every possible change has been rung on the amount of carbohydrate, protein and fat. There have been many opinions expressed about the "pros" and "cons" of normal or high blood sugar and the harmful or innocuous influence of glycosuria. To my mind, the basic principle that we should strive for in attempts at prevention of degenerative changes is the conservation of the body protein. Most diets will accomplish this. Obesity is a distinct enemy of tissue soundness, glycosuria will undoubtedly destroy tissue protein, the action of insulin, even in the presence of a high blood sugar and some loss of sugar in the urine, will conserve the body tissues. The physician treating diabetes should see to it that there is an adequate supply of glycogen in the liver, and that there is no excessive loss of nitrogen which loss indicates protein destruction in his patients. All of this has to be done according to theoretical knowledge since the chemical determinations necessary to effect this clinically are impossible under any conditions of treatment except those surrounding endowed research medicine.

There is one experience I should like to mention in closing. At Sea View Hospital for the treatment of tuberculosis we have a considerable number of diabetic patients. We found that those who were treated with Protamine Zinc Insulin reacted to their tuberculosis or recovered from it in a much more favorable manner than did those treated with the unmodified or regular insulin. We ascribe this to the fact that Protamine Zinc Insulin acts throughout the whole period of the twenty-four hours, whereas the unmodified insulin acts for stretches of four or more hours only. We felt that the tuberculous diabetic when not under the influence of insulin was subject to protein destruction and that under these circumstances his disease was more prone to progress than when under the constant protection of insulin which prevented such a process. It is probable that the diminishing occurrence of gangrene of the extremities, which I believe most physicians are experiencing, is due to the use of Protamine Zinc Insulin. It may be that the vascular lesions in the eyes will ultimately also become less frequent and less intense for the same reasons.

DR. FREDERICK M. ALLEN I certainly had not expected to say anything this evening. I think that after retinal changes have occurred, the outcome becomes doubtful—why this is so, I have no idea. In Polyclinic Hospital, a number of cases of retinitis do clear up under diabetic treatment and a number don't—the late cases are stubborn. When it comes to prevention of this complication, I regard the diabetic as

a normal individual who happens to be denied insulin—thinking must be done in the simple terms of insulin definitely—as mentioned by Dr. Bauman.

Three classes of patients come to us: (1) some come with complications already developed; (2) some are adequately treated but break their diet, etc. and come back with complications, and (3) some adhere strictly to their prescribed treatment and have no complications.

I have no theories on the subject. When a person comes to me without complications, I tell him that he will have no complication. I do not advise my patients to "wash their feet," etc., I tell them to treat their feet just as any normal person would. After thirty years of practice, I have not seen any complicated cases in adequately controlled patients but a good many of my patients are floating around, and if any of you should find one who has followed conscientiously but developed complications, let me know. I am satisfied with this record. There are various things we do know—during the era of malnutrition between 1914 and 1920 when we had some diabetics so starved for two weeks that they couldn't even get out of bed, no retinitis developed. Many lived for a year on as low as 10 grams of carbohydrate a day and about 50 grams of protein a day but no retinitis resulted from protein or carbohydrate starvation. These patients lived largely on fat. I don't see that fat is the responsible cause of retinitis.

We have heard about vitamin deficiencies—this is coming to be the trend of medicine, the finding of concealed deficiencies of one or more vitamin or hormone factors. I can't understand the state of mind which grasps every idea of deficiency except that of insulin disregarding the fact that insulin is one of the extremely vital hormones of the body.

A patient with normal urine but high blood sugar I give possibly ten or twenty units of insulin and he no longer has a high blood sugar. I try to treat diabetes on the basis of diet, and use insulin sparingly. I have tried giving big diets and big doses of insulin and it doesn't work so well.

DR. FREDERICK W. WILLIAMS In the light of what we have heard this evening there seems little that I as a clinician can add to this discussion. At the outset however, I must say that I am not in possession of such a perfect record as that of Dr. Allen. It would seem to me that all of the cases that I see in The Morrisania City Hospital and in my office are complicated in one way or another. Quite a number of the patients, however, do not have retinopathy when we first see them; some never develop it and in those who do develop it, diabetes control does not seem to influence its progress very markedly. Statistics seem to prove either side of the case in this problem. Our experience agrees with Dr. Sanford Gifford's in that our surgically complicated diabetics were in ninety-five per cent of cases complicated with retinopathy.

I have listened carefully this evening to find a

mention of the cause of retinopathy. There has been no proven cause offered but there were several suggested possible causes mentioned for example, arteriosclerosis, permeability of capillaries, vitamin deficiency, and fluid-electrolyte balance disturbance. This all leads me to emphasize that there has been great advance made in the study of diabetes. We now come to the realization that all of the complications occurring in diabetic individuals are not directly due to disturbed carbohydrate metabolism. Diabetes is now considered to be a metabolic disturbance with large implication and a disturbed sugar metabolism is but one feature. Associated with this disturbance in sugar utilization there may be disturbed fat metabolism, disturbed vitamin utilization, disturbed fluid and electrolyte balance and last but not least, disturbed protein metabolism. From our experience with surgical cases we feel that the diabetic does best if he utilizes in twenty-four hours between 150 and 200 grams of carbohydrate, if he is not dehydrated, if the fat of his diet is kept low enough to avoid acidosis, and if his protein intake is in the neighborhood of 100 grams. By assuring adequate carbohydrate utilization he spares his endogenous proteins from destruction, and the higher protein intake will assure his existence in a state of protein anabolism. A patient in protein anabolism is a much better surgical risk than is a patient in protein catabolism. This protein metabolic factor may also have its influence on fluid balance. Thus it is very difficult to place one's finger on one single cause of a given complication in diabetes. We have all stressed our "hunches." Dr. Anderson advocates low fat diet in the hope of preventing arteriosclerosis, Dr. Allen is an ardent exponent of strict control of the sugar metabolism. Dr. Mosenthal has had great stress on the effect of a chronic state of dehydration as a factor in tissue injury. At this time I should like to lay emphasis upon the protein metabolic state of the diabetic patient as a factor contributing to his complications. I personally believe that no one factor is at work in any case but most likely a combination of circumstances are operating as the cause. In conclusion, I would say that diabetic control is difficult to define because of the complicated ramifications of metabolism. No one single observation such as a fasting blood sugar can be used as a criterion for control. I wish to impress upon you ophthalmologists who are here that the internist is really gripped when he is asked to control the diabetes in preparation for operation and when the ophthalmologist comes in and at the turn of the hand becomes a metabolist, orders a fasting blood sugar, gets a report of 180 mg. and then postpones the operation because the blood sugar is too

high. Blood sugar is a variable. A single reading means little. It is the total picture that counts. For emphasis I would say again that diabetic control consists of first, adequate carbohydrate utilization, second, no dehydration, third, no acidosis, fourth, adequate vitamin intake, and fifth, positive nitrogen balance. These can never be determined by a single blood sugar observation, and I would suggest that the metabolic management of the case be left in the hands of the metabolist.

DR. ANDERSON: Since Doctors Bauman and Jacobi have no refutatory remarks to make, I want to thank our distinguished guests and speakers and discussors and to express the appreciation of the New York Diabetes Association for their participation in this evening's program. I shall adjourn the meeting shortly but shall first call on Dr. Gifford for any closing comments he wishes to make.

CLOSING REMARKS OF DR. GIFFORD: I am certainly going to take a great deal away with me and I hope I can take it back intact to Chicago and bring it up with the internists back home.

I think that no ophthalmologist believes that diabetes alone can't cause retinitis because we do see retinitis among patients who have no other signs such as hypertension or any other disease. We do know that it must be due to some diffuse vascular disease but it is certainly quite different from what we see in the ordinary type of arteriosclerosis. We feel that retinitis represents more than the ordinary type of diffuse vascular disease.

The results of a controlled series by Leopold in Philadelphia (published in the Archives of Ophthalmology) are very discouraging.

When I speak of capillary fragility, I am not thinking of a deficiency of Vitamin C. Freudenthal originally suggested this but later found that results were not good with Vitamin C administration and subsequently withdrew his original paper. Vitamin P is possibly a factor—it is available in concentrated form.

It is only by examination of a large number of diabetics for this fragility factor and the discovery of a successful means of forestalling or correcting it that we can ever hope to prevent this very serious complication—possibly the worst one in diabetes. We would like to find out more about the cause and treatment of capillary fragility if this is possible.

To Dr. Williams, I want to say that that's not "metabolism"—that's what is known as "specialization" and I hope we can get away from it in the future.

The meeting was then adjourned.

Leiomyosarcoma of the Stomach Presenting Four Cases

By

ANTHONY BASSLER, M D, F A C P, L L D
NEW YORK NEW YORK

LEIOMYOSARCOMA is generally presented in textbooks and articles on malignancy of the stomach in connection with carcinoma. In these the symptoms are described to be similar to carcinoma and no special details are offered suggesting that there are any clinical differences between the two. The following four consecutive cases suggest that this cannot be

standards, may be present throughout. Thus lactic acid and Boas-Oppler bacilli are not present or very slightly so. The opposite of these are present in carcinoma. (3) Positive blood in test meals and occult blood in stools are not present in continued ways as is common in carcinoma. (4) The anemia is not so definite or progressive, in fact may not be present to pro-



Fig 1 Leiomyosarcoma of the stomach showing mass formation in the pyloric region, general involvement of the stomach walls and irregularities along the greater and lesser curvatures and in the fundic region

taken completely, although there is much similarity between these two types of malignant conditions. Particularly in this difference from carcinoma are (1) The symptom of anorexia may not be so distinct, it being not uncommon to see cases partaking fairly well of foods even when marked involvement of the stomach is present and almost to the very end. (2) Hydrochloric acid while usually reduced from normal

nounced degrees even though the case is well advanced. (5) Loss of weight may be slower during the course of the disease, some cases looking quite well nourished to almost the end. (6) The cachexia, so characteristic of carcinoma, may not be present or if so only to slight and modified degrees. (7) Death is more liable to occur by way of massive hemorrhage than in carcinoma. (8) The average age may be some-

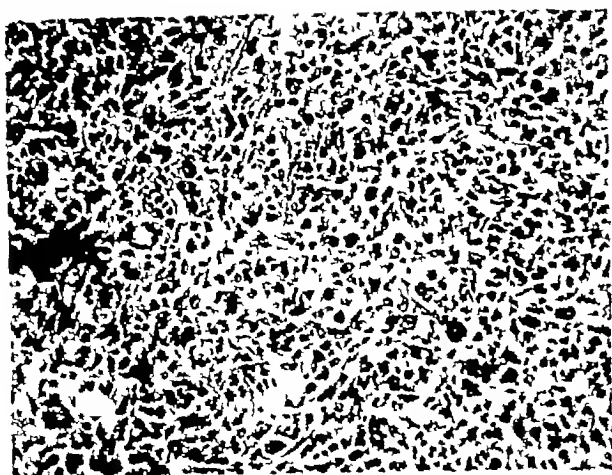


Fig 2, Case 3 Leiomyosarcoma of the stomach showing irregular arrangements of muscle-like bundle of cells and whorls, mitotic figures and atypism

what lower than in carcinoma, although this (like loss of weight) may be a questionable distinction (9) The abdominal mass is not liable to be so distinct or hard as seen in carcinoma, and (10) Pyloric obstruction is distinctly less liable to occur

CASE REPORTS

Case 1 S H (1937), male 37 years of age, operator on dresses, family and past history not being significant First observation made by the patient was a steady loss of weight, going from 149 to 127 lbs in six months time, appetite remaining fair all of the time Appearance of fair health No cachexia Soft, indefinite mass in gastric region Test meal, Free HCl 17°, total HCl 31°, total acidity 40°, no blood or lactic acid Hemoglobin 13.5 Gm, RBC, 4,100,000, WBC negative Icteric index 9 Feces, negative to blood X-rays showed a general stiffening of stomach wall, small serrations along curvatures, organ slightly enlarged, no pyloric obstruction negative shadow no gall stones, rest of examination negative Wassermann negative This patient lost weight rapidly in a space of four weeks, became markedly weakened, was hospitalized and on the fourth day had a marked hematemesis with continued vomiting of blood and was exanguinated in two hours Autopsy, leiomyosarcoma of the stomach

X-RAY

Case 2 V C Referred by Dr Knips, Manhasset, L I, (1941), 49 years of age 7 children Family and past history negative with the exception of having a chancre 10 years ago and was thoroughly treated in periods over several years of time the Wasserman test at one time becoming negative and at the time of my first examination was four plus Patient complained of loss of weight and appetite, slowly progressing over 3 or 4 months time The physical examination was negative with the exception of a mass (not especially hard) occupying the gastric region and more definite in the median line The blood showed a slight degree of hypochromic anemia, the feces negative to blood, and the test meal Free HCl 14°, total acidity 37°, no lactic acid or blood and slight excess of mucus The X-rays follow

Because the woman's general condition was good,

there being no cachexia, etc, the case was treated on the basis of it being a gastric syphilis with injections of bismuth and ascending doses of a saturated solution of potassium iodide and injections of iron citrate, these being continued for eight weeks without any improvement At the operation the entire stomach was involved with a grayish polymorphic lymphosarcoma or leiomyosarcoma The exploratory operation was followed by multiple deep roentgen treatments against which it was resistant Five weeks afterwards after a meal she suddenly vomited a large amount of blood followed by more quick voluminous vomitings of blood literally covering the bed and she was dead in an hour from exanguination

Case 3 M S, (1941), male, 39 years of age Family and past history not significant, excepting having complained of indigestion during three years which was variously diagnosed as peptic ulcer and not so The weight loss was but 8 lbs over 4 months time during which time he was more or less on a deficient diet and thus the weight loss was not considered important Six weeks before being first seen by me he had an intestinal hemorrhage (melena) accompanied by weakness, faintness, etc and followed by tarry stools for four days The patient had always been of the thin type, now showing distinct pallor and an anemia of hemoglobin of 11.4 Gm and RBC 2,700,000, morphology and WBC negative The test meal was Free HCl 12°, total acidity 27°, no lactic acid, but both test meal and stools were positive for blood suggesting a drip type of hemorrhage The stomach was felt as being somewhat stiffened, not tender and not presenting the character of carcinoma The X-rays suggested a stiffened organ, normal or perhaps somewhat enlarged in size, with no peristalsis and small serrations along the curvatures He was hospitalized followed a steady down-hill course, died of repeated hemorrhages and a pulmonary thrombosis At autopsy the stomach was completely involved with a leiomyosarcoma with metastases scattered about in the peritoneum and post abdominal wall

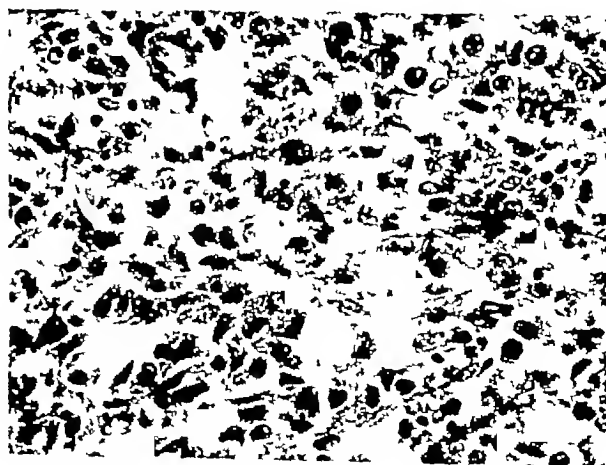


Fig 3, Case 4 Leiomyosarcoma of stomach showing a highly cellular tissue with faint background of fibrous tissue The cells are various, the predominating cell being large with a large nucleus and nucleolus Some cells are spindle-shaped and aligned stream-like Tiny fibrils scattered throughout Mitotic figures numerous Many large multinucleated cells

Case 4 (1942), male, clerk, 58 years of age. Family history negative. Past history three attacks of broncho-pneumonia. Tonsils and all teeth removed three years before for infections. The rest of past history not significant. Beginning about eight months ago had indigestion (pyrosis, distension and occasional partial vomiting). In the last four weeks had marked indigestion accompanied by anorexia. Thinks he may have lost a few pounds in weight but is not sure. Rather definite mass in epigastrium, also slight protrusion of the gastric region. Hemoglobin 90, RBC 4,100,000, WBC negative. Test meal Free HCl 0°, total acidity 11°, histamine response negative. Died in 3½ months after a series of hemor-

rhages. Autopsy general involvement of the stomach walls which were much thickened with masses in the pyloric region. Careful search for possible open lesion responsible for the bleeding was negative. There was a small follicular type of penetration near the greater curvature that passed through the mucosa.

CONCLUSIONS

Four cases of leiomyosarcoma of the stomach are briefly presented.

This type of malignant disease may present clinical symptoms somewhat different than the average case of gastric carcinoma suggesting that a more special description is worthy of consideration.

Proteus Vulgaris and Proteus Morganii in Diarrheal Disease of Infants

By

ERWIN R. NETER, M.D.

and

REGINALD H. FARRAR, M.D.

BUFFALO, NEW YORK

DIARRHEAL disease of newborns and infants represents one of the most important pathological conditions of childhood, because it is very common and has a relatively high mortality rate. Unfortunately, the present-day knowledge of the causes of enteritis, colitis, and like diseases is by no means complete. There can not be any doubt that in certain instances members of the typhoid-paratyphoid and dysentery bacillus groups are responsible for the infection. Suggestive evidence has been accumulating during the last few years which indicates that in certain epidemics a virus or virus-like agent may be responsible for diarrheal disease of the newly-born. In many cases, however, it has not been possible to establish with certainty the causative agent whether it be a bacterium or a virus.

Aside from the proven enteric pathogens a number of bacterial species have been incriminated as causative agents of intestinal disease. Among these are the members of the proteus group, *B. morganii*, *B. pyocyaneus*, and various species belonging to the paracolony group. However, it is still a moot question as to whether or not *B. proteus* and *B. morganii* play any role as primary incitants of enteric disease. On the one hand, these organisms have been isolated from patients with gastro-intestinal disease in which no other pathogenic micro-organisms were recovered. On the other hand, these species are encountered in healthy individuals without history of previous enteric illness. At the Children's Hospital, several cases of enteritis, colitis, and entero-colitis were observed which harbored *B. proteus* or *B. morganii* but no other pathogens in the feces. In the following com-

munication we should like to present the clinical and bacteriological data obtained in these cases and to discuss the question of the pathogenic significance of these species. Unfortunately no final answer to this problem can be offered.

METHODS

The technique used in the isolation of the intestinal pathogens has been described elsewhere (1). It suffices to mention that the stools were usually plated on three differential culture media, namely, Endo agar, MacConkey agar, desoxycholate-citrate agar. Non-lactose-fermenting colonies were then isolated and identified by means of fermentation tests. Glucose, lactose, sucrose, dulcitol, inositol, xylose, maltose, mannitol, and galactose were used in phenol red broth base (Difco). In addition the strains were tested for their capacity to liquefy gelatin and to form indole.

Sera obtained from the patients at various stages of the illness were examined for the presence of agglutinins. As antigens suspensions of the organisms isolated from the respective patients were used. The suspensions were prepared in 0.4% formaldehyde-saline solution. The tubes were incubated for 24 hours at 56° C and the results were read at various intervals. In some instances, parallel tests were carried out at 37° C.

Immune sera were prepared in rabbits. The respective bacterial suspension was injected intravenously. Two doses were given one week apart. The rabbits were bled eight days after the last intravenous injection.

RESULTS

The results of the clinical and laboratory observations obtained in twelve cases with enteritis, colitis, or entero-colitis, which harbored *B. proteus* or *B.*

*From the Children's Hospital and the University of Buffalo School of Medicine, Buffalo, New York.

Part of an investigation on enteric disease supported by the Statter Trust.

morganii, or both in the feces, are summarized in Table I. It is important to mention that all patients were infants under one year of age. This finding is all the more remarkable as this study was not restricted to infants, but included all patients at the hospital at the time of this investigation. All children had diarrhea and only in a few instances were blood and mucus present in the stools. In the majority of cases the temperature was above 100° F. Vomiting occurred in 7 cases. Three of the patients succumbed and nine recovered.

The twelve cases may be appropriately classified into three groups. Group 1 comprises three cases in which *Proteus vulgaris* was found in the feces. It is noteworthy that in one of these cases (E, F) this microorganism was found in seven out of nine stool specimens. In the remaining cases *B. proteus* was recovered on several occasions and was still present at the time when the diarrhea had subsided.

In order to elucidate the problem of the pathogenicity or non-pathogenicity of *Proteus vulgaris* in these cases, the antibody response of the patients was investigated. Sera were obtained at various stages of the illness. In spite of the fact that the serum of patient E, F was examined 5 and 15 days, respectively, after the onset of the illness, no agglutinins were found against the strain isolated from this patient. Essentially identical results were obtained in the other two cases whose sera were examined up to 1 and 4 weeks, respectively, after the beginning of the diarrheal disease. In these patients too, the homologous strains were used as antigens. In none of the cases was the titer of agglutinins higher than 1:10.

In order to ascertain whether or not this lack of antibody response in these patients is due to lack of antigenicity of the microorganism, immunization experiments were carried out in rabbits. The strain of *Proteus vulgaris* isolated from patient C, V was used. Two single injections sufficed to engender agglutinins in titer up to 1:1000. Thus, it is evident that the strain did not lack in antigenicity and that the failure of this child to develop agglutinins must be due to other factors. It will be discussed later whether or not this lack of antibody response indicates lack of pathogenicity of this microorganism.

The second group of cases is comprised of nine patients with enteritis or entero-colitis, in whose stools *B. morganii* type 1 was present. As may be seen from Table I, seven of the patients recovered. Two died, one from purulent meningitis complicating spina bifida. At the post-mortem examination the other presented the endstage of internal hydrocephalus and showed signs of entero-colitis.

It is interesting to note that in two of the seven cases *B. morganii* type 1 was isolated over periods of up to six weeks.

The antibody response was followed in three cases. None developed agglutinins against the homologous microorganism in significant titer. These negative results were obtained up to two months after the onset of the diarrheal disease. It is also noteworthy that the strain isolated from one of the patients readily engendered agglutinins in high titer in rabbits.

In the third group of cases are included two patients whose stools contained both *B. proteus* and *B. morganii* type 1 either simultaneously or on different

TABLE I
Cases with *B. proteus* in feces

	Age	Sex	Diarrhea	Vomiting	Fever	Antibody Response	Outcome	Concurrent Diseases
(1) C, V	3 months	M	+	+	+	—	Improved	Otitis media
(2) J, L	10 months	M	+	—	—	—	Improved	—
(3) E, F	2 months	F	+	+	+	—	Died	—

Cases with *B. morganii* in feces

(1) E, B	2 months	M	+	—	+	—	Improved	—
(2) S, H	7 months	F	+	+	+	—	Improved	Otitis media
(3) R, C	3 months	M	+	—	+	—	Improved	Cervical lymphadenitis
(4) L, P	3 weeks	M	+	—	+	—	Improved	—
(5) D, R	9 months	M	+	+	+	—	Improved	—
(6) J, K	16 days	F	+	—	—	—	Died from meningitis	Spina bifida
(7) J, B	7 months	F	+	+	+	—	Died	Int. hydrocephalus

Cases with *B. proteus* and *B. morganii* in feces

(1) J, F	3 months	M	+	+	+	—	Improved	Otitis media
(2) R, M	6 months	M	+	+	+	—	Improved	—

It is noteworthy that strains of either *B proteus* or *B morganii* could be isolated from one individual on consecutive occasions which proved to be biochemically identical, but differed in antigenic structure. It is possible that different strains of the same species were present in these cases, but it seems more likely that the isolated microorganisms actually represent variants. If this be the case, it would indicate that dissociation had taken place in the intestinal tract which, in part, may account for the lack of antibody response in these patients. In this connection it is interesting to mention that following feeding of a strain of *B morganii* type 1 to an infant (with very marked hydrocephalus in a hopeless condition) several strains were recovered from the feces which were culturally identical, but antigenically different from the original strain. This phenomenon deserves further study.

Although admittedly no definite conclusions with respect to the pathogenic significance of *B proteus* and *B morganii* in enteric disease can be drawn from the data available thus far, it seems justifiable to assume that in infants these organisms do not thrive merely as saprophytes. The possibility has to be considered that one and the same species may be harmless to adults and older children and potentially pathogenic to infants. It is worth remembering that the intestinal flora of newly-borns and young infants differs from that of older children. On the other hand, it is possible that the primary incitant of enteric disease in these cases is as yet unknown and that *B proteus* and *B morganii* thrive better in the inflamed intestinal tract and, therefore, may be more readily recovered from the feces of these individuals. Further investigations are required to elucidate this problem.

SUMMARY

(1) Twelve cases of enteritis, colitis, or enterocolitis are presented. In 3 patients *B proteus* was present in the feces, in 7 *B morganii* type 1, and in 2 both *B proteus* and *B morganii*.

(2) Three of the patients died, two from concurrent disease.

(3) All of the patients were less than ten months old.

(4) During the same period *B proteus* and *B morganii* were only rarely encountered in the feces of older children with diarrheal disease.

(5) With one single exception no other pathogenic enteric organisms were recovered from the feces of these patients.

(6) Although the strains of *B proteus* and *B morganii*, respectively, were biochemically identical, they differed in antigenic structure.

(7) Strains isolated from one individual on several occasions showed antigenic differences in spite of the fact that they were biochemically identical.

(8) In 8 of the cases the antibody response was followed. In no instance did agglutinins develop against the homologous microorganism (or microorganisms) in titer of 1:10 or above, even several weeks after the onset of the illness.

(9) Two representative strains of *B proteus* and *B morganii* readily engendered agglutinins in rabbits.

(10) Feeding of a strain of *B morganii* to an infant resulted in the appearance of this microorganism in the feces. However, the strains recovered differed in antigenic structure from the parent strain, biochemically, they were identical.

(11) The significance of these findings is discussed.

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The Colloidal Gold Reaction of Blood Serum in Hepatic and Other Diseases

By

PAUL H. NOTH, M.D., M.S.

and

EARL R. LOEW, Ph.D.

DETROIT, MICHIGAN

IT has been reported by Gray (1) that the blood serum of patients with hepatic disease is altered in some way so that it flocculates colloidal gold. He found that in 93% of ninety-six cases of hepatic disease a positive gold reaction was present. On the other hand, the incidence of positive reactions in ninety-five normal persons or patients with extrahepatic disease was only 2.6%. Sweet, Gray and Allen (2) found that the test was positive in eight of nine cases of hepatocellular degeneration. Bauer (3), using a different technical method previously had found that flocculation of colloidal gold solutions by blood serum occurred in some cases of hepatic cirrhosis and acute hepatitis, but not in any of eight patients with obstructive jaundice. More recently, Mateer et al (4) have published data related to a comparison of the colloidal gold reaction with other liver function tests. We have attempted to confirm the claims made by Gray and in many instances have compared the colloidal gold reaction with liver function tests now in general use. Data have been secured from a total of 245 patients with and without hepatic disease, and a group of twenty-five normal males. In nearly all cases, the patients were examined by the clinical author.

METHODS

The colloidal gold solutions employed in determining the reaction with blood serum were prepared according to the method outlined by Gray (1), important details of which were supplied in a personal communication (5). Meticulous care was taken in the preparation of glassware and reagents. As an additional precautionary measure, the standardization of each gold solution was rechecked every ten to fourteen days and the amount of acid required in conducting the tests was altered, if necessary.

In agreement with Gray (5), we found it necessary to use only three dilutions of serum (1:3,500, 1:7,000 and 1:14,000) in conducting each test. All sera were from samples of unhemolyzed blood. Tests were read eighteen to twenty-four hours after adding colloidal gold to the diluted sera. A positive reaction consists of a change from the original orange-red color to a light blue color (No. 4) or a colorless solution (No. 5) in one or more of the three tubes. A negative reaction is indicated by a change in color to red-blue (No. 1),

orchid or purple (No. 2) or deep blue (No. 3). All results are expressed by numbers which represent the various color changes which were obtained. For instance, negative reactions are those in which a series of three numbers do not contain a number 4 or 5.

The bromsulphalein test was performed by the intravenous injection of 50 milligrams of the dye for each kilogram of body weight, and the withdrawal of samples of blood at five, thirty, and sixty minutes after injection. Any retention of bromsulphalein at the end of one hour was considered abnormal.

The hippuric acid test was conducted by ascertaining the hippuric acid content of samples of urine collected at hourly intervals for four hours after the fasting patient had ingested 60 grams of sodium benzoate dissolved in water. It has been customary to express the results of the test in terms of the amount of sodium benzoate which was detoxified by the liver to form the amount of hippuric acid present in the urine. This is accomplished by multiplying the figures for hippuric acid by the factor 0.68. When the resultant figure was less than 2.75 grams the test was considered to be abnormal. In nearly all instances in which the hippuric acid test was abnormal, the blood urea was determined. If this was elevated, the hippuric acid was discarded.

In most instances the icteric index of the serum used for each colloidal gold test was determined. In some cases the serum proteins, serum phosphatase, plasma cholesterol, urinary urobilinogen (expressed as the highest dilution in which a positive test occurred) and prothrombin time (Quick) were measured. The normal value for prothrombin time varied from twelve to fourteen seconds. Normal controls were used in each determination.

RESULTS

Hepatic cirrhosis. Table I shows the findings in thirty cases of hepatic cirrhosis. In twenty-two cases an average of 3.5 tests were done during an average period of twenty-three days. The colloidal gold test was positive in twenty-seven or ninety per cent. As indicated in the table there were only a few instances in which the results of the various indices of hepatic function did not agree. This uniformity is partially explained by the advanced stage of the hepatic disease in most of these patients. In each of the three cases

*From the Departments of Medicine and Physiology of Wayne University College of Medicine and Detroit Receiving Hospital.

with negative colloidal gold tests the presence of hepatic cirrhosis was established by pathologic examination (Table III, Cases 6, 11, 13). The cirrhosis was graded as marked in one, moderate in the second, and slight in the third. Bromsulphalein and hippuric acid tests were done only in the last case and were both negative.

In seven cases serial bromsulphalein and/or hippuric acid tests were performed. The bromsulphalein test returned to normal in four cases. In one of these the hippuric acid test also resulted to normal, and in two it remained unchanged. The bromsulphalein test showed improvement in two other cases in one of which the hippuric acid test also showed improvement. The bromsulphalein test was not done in the final case in which serial hippuric acid tests showed some improvement. The improvement in hepatic function indicated by the bromsulphalein or hippuric acid test was usually apparent in the patient's physical condition as

Twenty-two of the twenty-nine cases gave positive colloidal gold tests on either the first or on subsequent occasions. Among the twenty-two cases there were seven in which the test was originally negative and later became positive. The jaundice was usually of less than one week's duration in these seven cases. Since the serial tests were not made at uniform intervals, it is impossible to state accurately the time required for the test to become positive, although as judged by the time of the appearance of the first positive test an average period of thirteen days elapsed. This change in the test did not parallel the clinical course since in all but one case the icteric index had decreased considerably by the time the test became positive.

Bromsulphalein tests were usually not done until the icterus had largely disappeared, because of the known inaccuracy of this test in the presence of an appreci-

HEPATIC CIRRHOSIS

		COLLOIDAL GOLD	
		POSITIVE—27 cases	NEGATIVE—3 cases
BROMSULPHALEIN EXCRETION	ABNORMAL	15	0
	NORMAL	<u>2</u>	1
HIPPURIC ACID TEST	ABNORMAL	13	0
	NORMAL	<u>1</u>	1
SERUM PROTEINS	ABNORMAL	20	<u>2</u>
	NORMAL	<u>2</u>	1
PROTHROMBIN TIME	ABNORMAL	10	<u>1</u>
	NORMAL	<u>2</u>	0
CONFIRMATION OF DIAGNOSIS	AUTOPSY	9	2
	BIOPSY	1	1
	OPERATION	2	0

* Underscored figures indicate variant results

Table I. The results of the colloidal gold test in hepatic cirrhosis as compared with other indices

well as in the levels of serum proteins, hemoglobin, and erythrocytes. Serial colloidal gold tests in these and fifteen other cases did not return to normal in any instance. In agreement with Gray we found insufficient evidence to indicate that alterations in the degree of abnormality of the colloidal gold test can be interpreted clinically. Therefore, only a return to normal is considered significant.

Acute and sub-acute hepatitis. There were twenty-nine cases in this group, in five of which the clinical diagnosis was confirmed by autopsy or biopsy (Table III). The types of hepatic present were as follows: Acute catarrhal jaundice, ten cases, toxic hepatitis, ten cases, acute hepatitis secondary to gall bladder disease, three cases, acute or sub-acute yellow atrophy, two cases, Weil's disease, two cases, suppurative hepatitis, two cases. In twenty of the cases an average of 4.3 tests were made during an average period of 23.7 days.

able degree of jaundice. This probably explains the fact that five of the six cases gave negative tests.

Hippuric acid tests were done in thirteen cases with positive results in eight. The average value of the icteric index at the time of the positive tests was 75, whereas the average icteric index at the time of the normal hippuric acid tests was 17. This illustrates a close relationship in these cases between the severity of the jaundice and abnormality of the hippuric acid test. The hippuric acid excretion returned to normal in two of three cases in which serial tests were done.

A reversal of the colloidal gold reaction from positive to negative occurred only twice in the twenty cases with serial tests. We have other evidence to indicate that this test may remain positive for long periods of time following an attack of acute hepatitis. Not included in the present series are the colloidal gold reactions of the blood sera of twenty-seven patients at the Lapeer State Hospital. These patients

were observed by Dr. Kenneth McLeod during an epidemic of catarrhal jaundice which occurred in the latter half of 1939. He kindly sent samples of their blood in January, 1941. Although these patients were stated to have no symptoms or physical signs of residual hepatic damage, the colloidal gold reaction was positive in twelve instances. Four patients with positive colloidal gold tests (and one with negative) had normal bromsulphalein tests.

Another patient had been in Receiving Hospital from November, 1937, to May, 1938, suffering from toxic adenomatous goiter, severe acute hepatitis and peripheral neuritis. His bromsulphalein test returned to normal by March, 1938. The hippuric acid test remained abnormal at this date, but was normal in August, 1938. In December, 1940, both the bromsulphalein and hippuric acid tests were normal, whereas the colloidal gold test was repeatedly positive. At this time although the patient had no complaints

crete any hippuric acid on two occasions, and a plasma cholesterol level of 126 mg per cent.

In two cases the originally negative colloidal gold test later became positive. In one patient with cholelithiasis the test became positive coincidentally with an increase in jaundice due to a complicating sub-hepatic abscess. The other patient had entered the hospital because of jaundice following the fifth injection of nearsphenamine. When first studied he presented a clinical picture typical of the syndrome of intrahepatic biliary obstruction described by Hanger (6). The plasma cholesterol level was 686 milligrams for each one hundred cubic centimeters, the serum phosphatase was 17 Bodansky units, the differential count of the leucocytes of the blood showed ten per cent eosinophiles, the stools were acholic, and the urine contained only traces of urobilinogen. At this time the colloidal gold test was negative on two determinations. The jaundice disappeared after about

CASES WITHOUT EVIDENT HEPATIC DISEASE WITH POSITIVE
COLLOIDAL GOLD TEST

DIAGNOSIS	BROMSULPHALEIN TEST NORMAL	HIPPURIC ACID TEST NORMAL	REMARKS
1. 2. TUBERCULOUS PNEUMONIA LATENT SYPHILIS			
3. TUBERCULOUS SALPINGITIS CHRONIC PYELONEPHRITIS	X		
4. PARATYPHOID FEVER		X	
5. ACUTE RHEUMATIC FEVER	X	X	SERUM PROTEINS NORMAL
6. CHRONIC RHEUMATOID ARTHRITIS SPLENO-MEGALY-POST-MALARIAL LATENT SYPHILIS	X		RECENT ARSENICAL THERAPY
7. ACUTE UPPER RESPIRATORY INFECTION LATENT SYPHILIS	X	X	SERUM ALBUMIN 3.3 GR. % JAUNDICE YEARS AGO
8. DERMATITIS VENEREALIS WITH SECONDARY INFECTION			
9. EXFOLIATIVE DERMATITIS DUE TO EITHER ARSENIC OR BISMUTH LATENT SYPHILIS	X		
10. NEUROSYPHILIS	X	X	
11. MYXEDEMA CARDIOVASCULAR SYPHILIS	X	X	SERUM ALBUMIN 3.3 GR. %
12. THROMBO-ANGITIS OBLITERANS CHRONIC ALCOHOLISM			
13. CHRONIC DUODENAL ULCER			GRAHAM-COLE SERIES NORMAL
14. INDETERMINATE DYSPEPSIA	X		ROENTGEN STUDY OF STOMACH AND GALL BLADDER NORMAL

Table II. Clinical diagnoses, results of other tests, and remarks concerning cases without evident hepatic disease in which the colloidal gold test was positive.

referable to the liver, and was apparently in good health. Physical examination revealed enlargement of the spleen.

Obstructive jaundice. The clinical diagnoses in six cases were as follows. Obstruction of the common bile duct due either to carcinoma of the head of the pancreas or to chronic pancreatitis, carcinoma of the pancreas, carcinoma of the stomach with biliary tract obstruction due to metastatic involvement of lymph nodes, choledocholithiasis, choledocholithiasis complicated by a sub-hepatic abscess, and arsenical hepatopathy of the type described by Hanger (6). The clinical diagnoses were confirmed by operation in three cases and by autopsy in one (Table III).

The colloidal gold test was originally negative in five cases and positive in one. The latter, a case of carcinoma of the pancreas in which jaundice had been present for several weeks, presented features of severe complicating hepatic damage such as failure to ex-

crete any hippuric acid on two occasions, and a plasma cholesterol level of 126 mg per cent. In two cases the originally negative colloidal gold test later became positive. In one patient with cholelithiasis the test became positive coincidentally with an increase in jaundice due to a complicating sub-hepatic abscess. The other patient had entered the hospital because of jaundice following the fifth injection of nearsphenamine. When first studied he presented a clinical picture typical of the syndrome of intrahepatic biliary obstruction described by Hanger (6). The plasma cholesterol level was 686 milligrams for each one hundred cubic centimeters, the serum phosphatase was 17 Bodansky units, the differential count of the leucocytes of the blood showed ten per cent eosinophiles, the stools were acholic, and the urine contained only traces of urobilinogen. At this time the colloidal gold test was negative on two determinations. The jaundice disappeared after about

two months, but recurred three months later following re-administration of arsphenamine when the entire picture was that of the usual type of arsphenamine hepatitis with decreased plasma cholesterol, urobilin present in the stools, and increased concentrations of urobilinogen in the urine. The colloidal gold test was then positive. Unfortunately, permission for a biopsy of the liver was not granted.

Hippuric acid tests were positive in three instances, in two of which the colloidal gold test was negative.

Primary and metastatic carcinoma of the liver. Of the eleven cases in this group, two were primary and nine metastatic. In six cases the clinical diagnosis was confirmed by autopsy or peritoneoscopic biopsy (Table III). The colloidal gold reaction was positive in seven, including both cases of primary carcinoma, in six of these either a bromsulphalein or hippuric acid test or both were performed and were positive in all instances.

The colloidal gold reaction was negative in four cases. In these the bromsulphalein test was done in two instances with one positive and one negative result. One hippuric acid test was positive. Autopsy in two of these cases showed relatively few carcinomatous nodules in one, but extensive metastases in the other.

Miscellaneous hepatic diseases. The nature of the hepatic disease in each of the four cases was proven by microscopic study of the liver (Table III). The colloidal gold reaction was positive in each of two cases in which the pathologic diagnosis was acute tuberculous hepatitis. It was repeatedly negative in a third case of generalized miliary tuberculosis in which the liver contained numerous tubercles. The fourth case was one of severe lipoidosis of the liver occurring in a patient suffering also from chronic alcoholism. The liver was very fatty and greatly enlarged, weighing 2850 grams. The colloidal gold test was negative, a bromsulphalein test was positive.

Cardiac failure with passive congestion of the liver. The colloidal gold test was positive in eight cases and was negative in twenty-three with hepatomegaly due to cardiac failure. Four patients with negative colloidal gold tests came to autopsy (Table III). The livers of two showed marked passive congestion, and the other two were essentially normal. Two further patients belonging to other groups had the incidental finding at autopsy of slight passive congestion of the liver. The colloidal gold test was negative in both. One patient with a positive colloidal gold test came to autopsy. The liver showed a moderate degree of chronic passive congestion.

There was no recognizable relationship between the severity or duration of the cardiac failure and the reaction of the test. Of six patients suspected of having cardiac cirrhosis three had positive and three had negative tests. There was also no consistent relationship among the results of the bromsulphalein, hippuric acid and colloidal gold tests. The bromsulphalein test was performed in thirteen cases with four positive and nine negative results. The hippuric acid test was performed in eight cases with four positive and four negative results.

Hepatic disease of indeterminate type. This group, twenty-four in number, is composed of cases with clinical or laboratory evidence of hepatic damage, the exact nature of which was indeterminate or difficult to classify. Among the eighteen miscellaneous cases with positive colloidal gold tests there were three of sickle-cell anemia, two of hyperthyroidism complicated by cardiac failure, and one each of congenital hemolytic icterus, pernicious anemia, beriberi, tuberculous polyserositis, tuberculous peritonitis, malaria, and other diseases. While many of these cases were interesting diagnostic problems, particularly as to the type of hepatic involvement the indeterminate nature of this negates the value of further comment. One patient suffering from myxedema, exfoliative dermatitis, and latent syphilis came to autopsy. Mild fatty meta-

morphosis of the liver was found. The colloidal gold test was negative.

Acute and chronic cholecystitis. There were twenty-one cases in this group, in twelve of which the diagnosis was confirmed by operation. A mild degree of hepatitis was probably present in some patients as indicated by the fact that the icteric indices were above 15 in nine cases, but not above 30 in any case. This degree of jaundice is common enough among patients with cholecystitis so that it does not seem necessary to consider it as a complication. One patient was found to have a common-duct stone, and the liver of another patient was slightly enlarged, otherwise the disease found at operation was limited to the gall-bladder.

There were only two cases in which the colloidal gold test was positive. Apparently uncomplicated chronic cholecystitis was present in one, and calculous cholecystitis was present in the other.

Patients without evident hepatic disease. This group, numbering ninety, is composed of patients who showed neither clinical nor any of the usual laboratory evidences of hepatic disease. Although icteric indices were done in all cases, only twenty-six patients had bromsulphalein and/or hippuric acid tests.

The colloidal gold test was negative in seventy-six cases. Included in this group are: Ten cases of miscellaneous types of mild acute infections, six cases of syphilis, five cases of pulmonary tuberculosis, five cases of malignant neoplasms, two cases of acute rheumatic fever, and one case each of arsenical dermatitis, dermatitis venenata, infectious mononucleosis, and polycythemia vera. These cases are mentioned chiefly because, in several instances, similar diagnoses were made in patients who had unexplained positive colloidal gold tests. In addition there were three cases of chronic glomerulonephritis, in two of which the ratios of serum albumin to serum globulin expressed in grams per one hundred cubic centimeters were 2.5:1.8 and 2.5:2.0. In one case of multiple myeloma with widespread amyloidosis of the muscles the serum albumin and globulin values were 3.5 and 1.2 grams respectively.

Table II shows the diagnoses and results of bromsulphalein and hippuric acid tests in the fourteen cases in which the colloidal gold test was positive. It should be noted that seven patients had syphilis, and two of these had received injections of neoarsphenamine a few weeks before. Eight patients had appreciable amounts of fever, frequently of long duration.

Autopsy and biopsy material. In thirty-nine cases included in the preceding groups the livers were studied pathologically, thirty-three at autopsy, and six by means of surgical biopsy. Table III shows data obtained in these cases.

It is of interest to note the behavior of the colloidal gold test when these cases are divided into four groups according to the amount of pathologically demonstrable hepatic damage—severe, moderate, slight, and

TABLE III
Data in pathologically studied cases

Group	Case No	Clinical Diagnosis	Pathological Description of the Liver	Coll Gold	Brom. Retent. % 1 Hr	*Hipp Acid	Other Tests
Hepatic cirrhosis	1	Portal cirrhosis Ruptured oesophageal varix	Weight 1340 G Advanced portal cirrhosis	548	20	1.44	Serum albumin 2.5 G % Serum globulin 2.1 G %
	2	Portal cirrhosis	Weight 970 G Chronic hepatitis (atypical cirrhosis) with organizing focal necrosis	532		0.00	Serum alb 1.9 G % Serum glob 3.0 G % Prothrombin time 24 sec
	3	Hepatic cirrhosis Calculous cholecystitis Bronchopneumonia	Weight 2220 G Advanced portal cirrhosis	553		1.4	Serum alb 2.6 G % Serum glob 2.4 G % Prothrombin time 16.4 sec.
	4	Portal cirrhosis Isoriase Latent syphilis	Weight 1360 G Advanced portal cirrhosis	553	20	2.66	Serum alb 3.1 G % Serum glob 3.5 G % Prothrombin time 13.6 sec.
	5	Portal cirrhosis	Weight 2020 G Advanced portal cirrhosis	553	20	0.99 ²	Serum alb. 3.1 G % Serum glob 3.5 G % Prothrombin time 19 sec
	6	Portal cirrhosis with ruptured oesophageal varix	Weight 2100 G Portal cirrhosis. Very little normal appearing hepatic tissue Advanced fatty metamorphosis fibrous connective tissue increase and bile duct proliferation	222			Serum alb 2.5 G % Serum glob 2.0 G %
	7	Portal cirrhosis with ascites superimposed acute hepatitis	Hobnail liver Great increase in periportal connective tissue	543			Icteric index 81
	8	Chronic rheumatic heart disease with mitral stenosis	Passive congestion with extensive central necrosis Low grade portal cirrhosis Liver weight 2230 G Cuts with fibrous resistance	432			Icteric index 21
	9	Portal cirrhosis Hypertensive cardiovascular disease	Advanced portal cirrhosis	553	15		
	10	Chronic cholecystitis and cholelithiasis	Hepatic cirrhosis—mixed portal and toxic	553			Prothrombin time 18.5 sec Serum alb 1.7 G % Serum glob 3.2 G %
	11	Cardio-vascular syphilis Carcinoma of colon	Portal cirrhosis grade 2 (on basis 1-4) Chronic peri hepatitis	322			Prothrombin time 17 sec Serum alb 3.0 G % Serum glob 1.9 G %
	12	Portal cirrhosis possibly with complicating primary hepatic carcinoma	Biopsy Chronic hepatitis not typically portal cirrhosis Malignant neoplasm not definitely ruled out	543	40	1.6	Prothrombin time 17 sec. Serum alb 2.5 G % Serum glob 3.2 G %
	13	Chronic calculous cholecystitis Chronic hepatitis Alcoholism	Biopsy Cirrhosis Lobular tissue not especially damaged	322	0	3.16	Serum alb 4.0 G % Serum glob 2.0 G %
Acute and sub-acute hepatitis	14	Pneumococcal pneumonia Toxic hepatitis	Liver essentially normal	222		1.95	Icteric index 25 Urine alb trace. Sp grav 1.01 Blood urea not done
	15	Carcinoma of the stomach Pulmonary abscess and empyema	Toxic hepatitis	433			
	16	Acute bacterial endocarditis due to streptococcus hemolyticus	Heavy infiltration of polymorphonuclear cells in the sub-capsular area about the portal spaces and extending out into the lobules Frank necrosis of liver cells is present in only a few small areas	232			Icteric index 61.0
	17	Acute bacterial endocarditis due to staphylococcus aureus	Numerous areas of grayish necrosis up to 60 mm. in diameter (Abscesses also in myocardium kidneys, spleen)	111			Icteric index 8
	18	Chronic calculous cholecystitis Gangrene of gall bladder	Biopsy Tho hepatic cells near the capsule have a granular appearance and are undergoing hydropic change Chronic peri hepatitis	553			Icteric index 33 Prothrombin time 23 sec
Miscellaneous hepatic disease	19	Generalized miliary tuberculosis	Acute tuberculous hepatitis	443			
	20	Tuberculosis of the spleen and liver Latent syphilis	Operative biopsy Acute tuberculous hepatitis	532		2.54 (later) 1.15	Icteric index 15 Serum alb 4.1 G % Serum glob 2.3 G %
	21	Bilateral bronchopneumonia (autopsy showed acute generalized miliary t. b.)	Microscopic section shows numerous miliary tubercles	322			Icteric index 11

TABLE III CONTINUED
Data in pathologically studied cases

Group	Case No	Clinical Diagnosis	Pathological Description of the Liver	Coll Gold	Brom Retent. % 1 Hr	*Hipp Acid	Other Tests
Miscellaneous hepatic disease (cont)	22	Probable hepatic cirrhosis Chronic alcoholism	Weight 2850 G Severe lipofuscinosis with some intralobular necrosis. Some increase in the amount of portal connective tissue.	222	25		Prothrombin time 16 sec. Icteric index 15
Neoplasm of liver	23	Carcinoma of the stomach with hepatic metastases	Weight 1580 G Several yellowish white nodules largest 4.0 cm in diameter. Five or six smaller nodules. Adenocarcinoma grade 2.	223			Icteric index 35
	24	Carcinoma of the stomach with hepatic metastases	Over the surface and throughout the entire parenchyma are multiple small nodules up to 3.0 cm in diameter.	222	10		
	25	Carcinoma of the breast with hepatic metastases	Weight 3470 G Carcinomatous nodules practically replace all hepatic tissue.	555		0.511	Icteric index 24
	26	Carcinoma of the liver probably metastatic possibly primary. Latent syphilis.	Primary carcinoma of the liver hepatoma type.	532	15	3.3 2.05 1.62	Icteric index 21 Prothrombin time 18 sec
	27	Carcinoma of the colon with hepatic metastases	Peritoneoscopic biopsy. Several nodules in both lobes. Adenocarcinoma grade 1.	432	15	2.2	
	28	Hepatic cirrhosis with superimposed primary carcinoma	Weight 1000 G Hepatoma with cirrhosis.	555			Icteric index 60
Indeterminate hepatic disease	29	Mixedema Exfoliative dermatitis. Latent syphilis.	Fatty metamorphosis of central portions of lobules. Slight polymorphonuclear and eosinophilic infiltration of the parenchyma.	221			Icteric index 4
Congestive heart failure	30	Hypertensive and arteriosclerotic heart disease	Weight 1830 G Nutmeg appearance. passive congestion grade 1.	132			Icteric index 7
	31	Arteriosclerotic heart disease with myocardial infarction	Weight 2200 G Marked chronic passive congestion with central necrosis of liver tissue.	111			Urinary urobilinogen highest positive dilution 1/50
	32	Chronic rheumatic heart disease. Sub acute bacterial endocarditis.	Mild chronic hepatitis. Parenchyma essentially normal.	222		1.94	Blood urea 32 mg %
	33	Chronic pneumonia. Cor pulmonale.	Weight 1650 G Early nutmeg appearance. Chronic passive congestion of moderate degree with atrophy of central part of lobules.	554			Icteric index 6
	34	Chronic rheumatic heart disease with mitral stenosis. Recurrent congestive failure. Probable cardiac cirrhosis.	Biopsy. Very minimal increase in periportal connective tissue. Parenchyma appears normal.	221	0	2.07 2.74 3.25	Icteric index 9. Blood urea 24 mg % Prothrombin time 15.8 sec. Serum alb 3.6 G % Serum glob 1.5 G %
Obstructive jaundice	35	Cholelithiasis with sub hepatic abscess.	Weight 1600 G Increase in connective tissue about portal spaces and proliferation of duct epithelium. Mild pslephlebitis.	433			Icteric index 240
Patients without evident hepatic disease	36	Multiple myeloma. Amyloidosis of muscles. Bronchopneumonia.	Gross and microscopic appearance normal.	221	0		Serum alb 3.5 G % Serum glob 1.2 G %
	37	Chronic alcoholism. Thiamin deficiency neuritis. Possible beri beri heart disease.	Weight 1850 G Surface smooth. Moderate chronic passive congestion.	221	0	3.0	Icteric index 10
	38	Ruptured gastric ulcer. Bronchopneumonia.	Weight 1650 G Cloudy swelling and edema.	221			Icteric index 7
	39	Chronic pyelonephritis with uremia. Bronchopneumonia. Latent syphilis.	Weight 1800 G Chronic passive congestion with central lipofuscinosis.	111			

*Grams of hippuric acid expressed as sodium benzoate.

none. Severe hepatic damage may be considered to have been present in seventeen cases (1-7, 9, 10, 12, 19, 20, 22, 24-26, 28). In fourteen of these cases the colloidal gold test was positive, and in three it was negative. A moderate degree of hepatic damage is considered to have been present in eleven cases (8, 11, 15-18, 21, 27, 30, 31, 35). In five of these cases the test was positive, and in six it was negative. Slight hepatic damage was present in seven cases (13, 23, 29, 33, 37-39). The colloidal gold test was positive in one and negative in six. An essentially normal liver was present in four cases (14, 32, 34, 36), and the test was negative in all.

A summary of the pathological findings in cases in which the colloidal gold test was negative reveals that there were three cases with marked hepatic damage (one each of advanced portal cirrhosis, severe lipoidosis, extensive metastatic carcinoma), six cases with moderate hepatic damage (moderate portal cirrhosis, two cases of purulent hepatitis secondary to acute bacterial endocarditis, and of marked passive congestion of the liver secondary to cardiac failure, one case of miliary tuberculosis with moderate hepatic involvement), and six cases with slight hepatic damage (one case each of hepatic cirrhosis, metastatic carcinoma of the liver, mild fatty metamorphosis, cloudy swelling, and two cases of slight passive congestion).

It is also of interest to note the comparative behavior of the bromsulphalein and hippuric acid tests in these cases. Among the twenty cases with positive colloidal gold tests bromsulphalein tests were done in seven and were always positive. Hippuric acid tests were done in ten cases and were all positive except for the first test in one case which was negative at a time when the colloidal gold test was positive. The subsequent hippuric acid tests showed progressively increasing amounts of functional impairment.

Among the nineteen cases with negative colloidal gold tests bromsulphalein tests were done in six with two positive and four negative results. The positive tests were in patients with marked hepatic involvement. Two of the negative tests occurred in patients with slight hepatic involvement, and two in patients with no hepatic involvement. Hippuric acid tests were done in five cases with two positive and three negative results. The negative results occurred in two patients with slight hepatic involvement, and in one with a normal liver. The positive tests both occurred in cases in which the liver was anatomically normal. Clinical circumstances in both of these cases were suggestive of at least functional hepatic damage.

Normal males. The subjects in this group were twenty-five medical students or faculty members who gave no history of hepatic disease and who considered themselves to be in good health. The colloidal gold test was negative in all.

COMMENT

It often has been emphasized that the best index of the status of the liver is obtained by measuring as many of its functions as possible. Strictly speaking

the colloidal gold reaction is not a liver function test since it does not measure quantitatively any known function of that organ, however, the liver plays an important part in the manufacture of serum proteins, and it is apparently their alteration in hepatic disease which is responsible for the increased flocculation of colloidal gold solutions. Our data agree with Gray's in indicating that neither a quantitative alteration in total protein nor a change in albumin/globulin ratio is primarily responsible for this phenomenon since these determinations were normal in some cases with a positive colloidal gold test and were abnormal in some cases with a negative colloidal gold test. Gray (1) has reviewed the evidence pointing toward a qualitative change in the globulin fraction as the probable cause of positive colloidal gold reactions.

A further comparison between Gray's and our data reveals similarities and differences. In both series of cases there was a high incidence of positive colloidal gold reactions in hepatic cirrhosis, however, we found three such cases in which the test was negative, whereas it was positive in all of Gray's cases. The incidence of positive tests was definitely lower among our patients with acute and sub-acute hepatitis. The tendency toward negative tests among our patients with early or uncomplicated obstructive jaundice is in accordance with Gray's results in similar cases. In carcinoma of the liver we also found that positivity of the test usually depended upon the extent of the hepatic involvement, however, one of the negative tests occurred in the presence of extensive diffuse neoplastic disease of the liver (Case 24, Table III). The one recognized instance of severe lipoidosis of the liver, so diagnosed at autopsy (Case 22, Table III), was associated with a negative colloidal gold test while in Gray's two cases with pathologic findings of marked fatty degeneration of the liver the colloidal gold test was positive. Our group without evident hepatic disease showed a 15.5% incidence of positive colloidal gold tests whereas in Gray's group with various extra-hepatic diseases the test was positive in only 2.6%, however the two groups are differently constituted. We included patients with syphilis, but without evident hepatic disease, whereas Gray excluded all patients with syphilis because of his suspicion that this disease may alter the reaction between the blood serum and colloidal gold solutions. We had thirteen patients with syphilis but without evident hepatic disease, in seven of whom the test was positive. Further a larger proportion of our group suffered from febrile illnesses which were frequently of long duration, and which may have resulted in disturbances of hepatic function which were not evident clinically and were not reflected in other laboratory tests. We have observed the rather frequent occurrence of positive colloidal gold tests among patients suffering from pneumococcal pneumonia (unpublished data). Of one hundred six such cases, the first colloidal gold test was positive in fourteen, in twenty-eight others it became positive subsequently, and in

sixty-four cases it remained negative. However, in the last group the average number of tests obtained (3.1) was smaller than in the second group (4.2). The etiology and clinical significance of positive colloidal gold tests in febrile illnesses remains unestablished, but we feel that for the present these instances should be considered as unexplained positive reactions rather than as false positive reactions.

Certain observations regarding the behavior of the colloidal gold test in serial determinations are of interest. The tendency of this test to remain positive in cirrhosis and in acute hepatitis after bromsulphalein or hippuric acid tests have returned to normal has been mentioned. With the exception of the cases of catarrhal jaundice occurring at the Lapeer State Hospital and the one case of toxic hepatitis, the period of observation has been too short to critically evaluate what may be an important index of the persistence of hepatic damage. On the other hand, we have entertained the entirely speculative idea that abnormal serum proteins or protein-linked substances may be formed during episodes of hepatic disease and then, in some instances, persist for long periods, as in the case of certain immune bodies.

The finding that the colloidal gold test is frequently negative early in the course of hepatitis, becoming positive sometimes after a considerable interval, imposes definite limitations upon its usefulness as an aid in the differential diagnosis between hepatitis and obstructive jaundice, since it may behave similarly in both.

Since the number of bromsulphalein and hippuric acid tests was considerably smaller than that of the colloidal gold tests, an exact comparison of their sensitivity cannot be made. Analysis of the groups with well-defined types of hepatic disease reveals that in certain instances the colloidal gold test was positive when bromsulphalein or hippuric acid tests were negative but that the reverse situation also occurred with approximately equal frequency. In the present series there is no definite evidence that the colloidal gold test is more sensitive than the other tests employed. In the great majority of cases of well-defined types of hepatic disease, the tests agreed. This was not true for the groups with hepatic disease of indeterminate type or with passive congestion of the liver, in both of which there was little correlation between the results of the three tests. This may be explained by the fact that usually the liver was not as badly damaged in these groups, and that the different functions reflected by these tests may not have been uniformly affected.

The occurrence of negative colloidal gold tests in a number of cases in which mild or even moderate hepatic damage was found on pathologic examination should not be considered to be a condemnation of the

test, but rather just another demonstration of the great reserve power of the liver.

We believe that the "false positive" reactions found by Mateer et al. (4) among normal individuals were probably due to differences in their technique, which also vitiate the value of a comparison of our results with theirs. We feel that the performance of the test presents no difficulties which could not be surmounted by a technician familiar with the behavior of colloidal gold solutions as employed in testing spinal fluid.

SUMMARY AND CONCLUSIONS

A series of 155 patients with hepatic or biliary tract disease, ninety patients without evident hepatic or biliary tract disease, and twenty-five normal males were studied for the purpose of evaluating the reaction between blood serum and colloidal gold solutions as an index of hepatic disease. Pathological examination of the liver was performed in thirty-nine cases. The test was positive in twenty-seven of thirty cases of hepatic cirrhosis, and in twenty-two of twenty-nine cases of acute hepatitis, and in varying proportions in other types of hepatic disease. It was infrequently positive in obstructive jaundice and uncomplicated cholecystitis. Positive reactions were not encountered with sera of twenty-five normal males, but occurred in fourteen of ninety cases in which hepatic disease could not be demonstrated by physical examination or by other laboratory tests which were employed. Syphilis was present in seven of these fourteen cases and in eight, including four of syphilis, there were appreciable degrees of fever, frequently of long duration. In cases of cirrhosis and acute hepatitis, the test usually remained positive after bromsulphalein and hippuric acid tests had become negative. In well-defined instances of hepatic disease it was occasionally positive when the latter tests were negative, although the reverse situation also occurred. The test was negative in nine instances in which there were pathologic findings of marked or moderate hepatic damage, and in six instances in which slight hepatic pathology was present. On the other hand, it was negative in each of four cases in which pathologic examination revealed a normal liver.

It is concluded that although in our cases the test was not exceedingly sensitive in most circumstances, both its persistent positivity in cirrhosis and hepatitis and its positivity in certain febrile diseases in which other tests of liver function may be negative warrant further investigation.

We gratefully acknowledge our indebtedness to Commander O. A. Brines, U. S. N. (formerly Attending Pathologist of Receiving Hospital) for his reviewing of the pathological material, to Dr. Gordon B. Myers, Professor of Medicine, Wayne University, for helpful advice and suggestions; and to Mrs. Virginia Weeks and Mrs. Camille Hubel for generously given technical assistance.

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Primary Constipation Treatment*

By

DAVID C DITMORF, M D,
BOSTON MASSACHUSETTS

INTRODUCTION

A SIMPLE classification of constipation and a rational program of treatment is the subject of this paper (1) The average physician, wishing to increase his knowledge of the subject, quickly becomes aware of the confusion which exists and soon discontinues his investigation As an easy solution of his problem he prescribes some proprietary remedy which for a time produces results, and thus creates a nationwide market for oils and laxatives, the so-called health foods, and other products of purely commercial manufacturers

A careful analysis of our case histories shows that constipated patients fall naturally into one of three groups First, the group where the condition is *not* caused by disease. This is the principal theme of our paper and is referred to as Primary Constipation Second the group where the condition is caused by disease And Third the group where the condition is not caused by disease, but where it is aggravated by disease The last two are to be considered adjunctive to our theme, and should be discussed separately, each under its own text, at some future time

The diagnosis of Primary Constipation presupposes a most careful history and examination It hardly seems necessary to emphasize that any condition which may tend to irritate the anal ring, thus causing the sphincter to contract abnormally, is a definite factor in the cause of constipation (2) Anal fissure, hypertrophied papilla, repeated external thrombosed hemorrhoids, and protruded or protruding internal hemorrhoids are frequent offenders It should be remembered, too, that simply removing gross lesions may not mean that the spastic anal sphincter will relax, a moderate dilation may be necessary (3) Regardless of the age of the patient, pain (however mild or severe), blood or pus (whether just a trace or in copious amount), mucus in perceptible quantity, or sudden change in bowel habit indicate the presence of pathology X-ray diagnosis of spastic or atonic bowel may be ignored (4)

After necessary studies have been made and all organic trouble has been eliminated, we are justified

in making a diagnosis of Primary Constipation and proceeding with treatment. Adequate fluid intake, adequate food intake, adequate saline intake, chemotherapy and expert supervision are the necessary armamentarium.

DISCUSSION

Advice to patients to drink six to ten glasses of water daily has proven a failure in such a high percentage of cases that even the usually conservative editorial department of one of our largest and most respected journals recently wrote disparagingly of its efficacy (5), and Alvarez thinks he has seen it do actual damage (6) The truth is that we have in water a most useful adjunct in the treatment of constipation (7), but have failed to use it to the best advantage.

In the first place, it renders the bowel content more fluid, and therefore more easily pushed along by peristaltic action It is this property, generally recognized, which has in the past motivated the physician when prescribing fluids Poor results have followed because one glass of water taken at half hour or hourly intervals disappears from the bowel so quickly in many cases that only the proximal portion of the fecal stream is affected Proof of this is frequently observed in the hard, dry, impacted feces palpable in the rectum, in spite of the fact that the individual is drinking quantities of water daily On the other hand, the patient may not absorb rapidly, and the consequence is a continual arrival of liquid in the rectum and a resulting diarrhoea (8)

The second property of water is that it aids in providing bulk and thus stimulates peristalsis (9) This is a less important action, and when given by mouth we cannot depend upon it because the fluid is in most cases quickly absorbed Foods which form bulk are more dependable

The third and most important action of water used in the treatment of constipation is its property of carrying everything with it, if a sufficient quantity is applied over a short period In other words, the force produced is in direct proportion to the elevation of the reservoir supplying the liquid and the quantity available It varies inversely with the size of the lumen of the conveyor and the amount lost on the way to the rectum

Unfortunately, as previously indicated, individuals

*From the Department of Proctology Boston University School of Medicine and the Massachusetts Memorial Hospitals.
Instructor in proctology Boston University School of Medicine
proctologist, Massachusetts Memorial Hospitals

vary in their ability to absorb fluids from the bowel, so that no definite quantity can be established as just the proper amount needed in every case. We have found, however, that four ordinary glasses of water, or approximately one quart, given in divided doses before breakfast, over a period of not more than one-half to one hour, is usually sufficient, and that in many cases only one, two, or three glasses are necessary. We would, therefore, make this the first requirement in the treatment of constipation.

Patients are frequently astonished that they should be asked to drink so much water before breakfast, but any sensation of fullness is absent or quickly disappears, and they are happy when prompt and satisfying results are observed. Indigestion or flatulence, and, of course, nocturia, do not occur. As Alvarez has observed, diarrhea may develop (10), but that is not a problem since it means only that too much water has been taken, and the condition is corrected when the intake is reduced. We simplify the intake problem so that little or no extra time or effort is consumed in performing the morning toilet. The patient is told to take the water from the cold faucet, inasmuch as many hesitate to drink from the ordinary warm storage tank and any effort to obtain freshly heated water is time-consuming and after a short while becomes a burden. Also, fluids leave the stomach immediately (11) and temperatures are quickly equalized (12), so that for our purpose cool water is probably as efficacious as warm water. It is emphasized that all the water should not be taken at one time, because few would follow such advice and fewer still would continue it for long.

The second and very important requirement in the treatment of constipation is the adequate use of residue-producing foods (13). To obtain this, the patient is instructed to eat at least two cooked vegetables twice daily. It is emphasized that this means true vegetables, and any of them with the exception of tomatoes, potatoes, salads, and vegetable soups. Tomatoes are excluded because of the fluid content, and potatoes because they are used as additional bulk. Salads are excluded because most of them are cold and their bulk content likely to be limited by a small serving. Vegetable soups are excluded because certain individuals will substitute them for an adequate vegetable serving. In other words, salads, tomatoes, potatoes, and vegetable soups must not be substituted for cooked, leafy, or fibrous vegetables. When the patient understands clearly about eating the two vegetables twice daily, he is then told to eat anything and everything in addition that he desires.

A third and very useful adjunct in the treatment of constipation is additional amounts of ordinary table salt (NaCl) (14). Alvarez suggested that if one-quarter teaspoonful is added to a glass of water before breakfast, gratifying results are often observed (15). In the severely constipated patient we always advise its use, and results are pleasing. The fact that

an unlimited intake of NaCl is contraindicated in some diseases should not prejudice us against its use in normal individuals. It should be obvious that certain people require more salt than others, and that its use simply as a seasoning for foods may be insufficient in some cases. We have been under the impression, too, that the so-called "constitutionally inadequate" individual sometimes obtains more benefit than is reasonable to explain simply because regularity in bowel habit is established, and have wondered if there could be some relationship between this improvement and the increase in well-being frequently seen when salt is given in large amounts to the person afflicted with Addison's disease.

The fourth step in the treatment of Primary Constipation, and the one having fewer factors in its favor, is the use of (1) laxatives, (2) purges, (3) lubricants, and (4) bulk-producing products—in other words, chemotherapy. Laxatives and purges are mentioned only to be condemned. The so-called bulk-producing products have at least three disadvantages: some seem to be irritating, all soon lose their effectiveness (16) and, most important of all, they supply no more bulk than can be obtained from a sufficient quantity of nourishing vegetables. Of the lubricants, mineral oil by mouth seems to be the least objectionable (17). It is inexpensive. The individual is rare who enjoys taking it, and since it is intended as an immediate remedy, the physician is assured of his patient's cooperation. Given by rectum, it must be injected by means of the filthy bulb syringe or the equally filthy enema tip, terminating eventually in the infected, fissured, excoriated anal canal, with the attendant spastic or patulous anus so frequently seen in the proctologist's office. There is also the likelihood of habit formation, which produces the patient who never goes through the day without injecting a little lubricant so that he may pass a nice, soft stool.

We prescribe mineral oil in tablespoonful doses, when needed, to be taken by mouth before meals, and never at bedtime. It is needed before each meal if there has been no previous movement that day. The indications are exact. It is not taken before any meal which has been preceded by defecation. Its action has been questioned (18) but it seems logical to assume that massage of the bowel by movements of the body, and the upright position, favor its mixture with the fecal stream and passage distally. We have observed that a smaller dose, taken before meals, will accomplish the same result as a larger dose taken at bedtime. Leaking and too frequent movements do not occur unless too much oil is being taken, and the amount must be cut down until only one or two movements result. We have seen patients who complained of leakage accompanied by fifteen or sixteen bowel movements daily without fecal material. In nearly every case it is clear that they are taking oil in excess of the required amount, as evidenced by the fact that the lower sigmoid and rectum are clean, and that

no preliminary preparation is needed for the sigmoidoscopic examination

SUMMARY

The foregoing is an overall program which will produce satisfactory results in the most obstinate cases of Primary Constipation

In mild cases, good results are frequently obtained when the patient is instructed to take only the water and vegetables, or it may be necessary to add the salt or even the mineral oil

In extreme cases, in order to gain the confidence of his patient, the physician may outline the entire anti-constipation program in the beginning, and when he finds the patient having too many movements he can cut down first on the oil then on the salt, and later on fluid or diet, but one at a time, until only one defecation daily is achieved

Very frequently, in long-standing and obstinate cases the defecation reflex has been so increased (19) that the individual is not aware that a bowel movement is imminent until great pressure is exerted. Therefore when the regimen is first started, he should be told to be on the alert for vague symptoms of fullness in the rectum. He may wonder if he should try to have a movement. In case this occurs and it frequently does soon after the water has been taken

he should at least go to the toilet to see what will happen. No straining is needed. If he delays, the effect of the water may be lost and movement will not take place until later in the day, or not at all. As his habit becomes established, the threshold of the defecation reflex is lowered and an unmistakable urge will be present.

The busy family physician may feel that this program is too involved. We do not find it so, although it is sometimes necessary to question the patient at length in order to find in just what respect instructions are not being followed. Many persons who have taken laxatives and enemas all their lives seem to take a fiendish delight in proving their doctor wrong but we have found that a little persistence and patience give brilliant results in a high percentage of cases. During the past five years, prescriptions for laxatives have been almost eliminated in this clinic and in our private practice.

CONCLUSIONS

1 Primary Constipation is a term which describes adequately that condition which is not secondary to disease

2 Proper management of fluids, food, salt and mineral oil will eliminate the complaint in almost every case

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Notes On Nutrition

Food Problems of Free China While China is to be admired for having had over a period of forty centuries a somewhat inadequate agricultural system, nevertheless, it is known from surveys made before the Japanese invasion, that China's food was lacking and that the following conditions were prevalent in many sections — xerophthalmia, night blindness, urinary calculi, hyperkeratosis, osteomalacia, rickets, tetany, avitaminosis C, ariboflavinosis, beriberi, pellagra and nutritional edemas and anemia. Startling increases in the incidence of nutritional diseases between 1937 and Pearl Harbor were found in East China.

Free China's food problem is complicated by the feeding of 14 million men in the armed forces, by the care of refugees from the East, by the effects of the

scorched earth policy and finally by the inflation which has raised the cost of living 60 fold, or 6 000 per cent above 1937 levels. The increase in general morbidity and especially tuberculosis is tragic. The middle classes are affected as never before and the quality of food, as well as its quantity, is below normal. Dairy products are almost absent from the diets, transportation is meager and there is no refrigeration for perishables. Farmers sell rice at high prices so that cattle are not fed and there is a dearth of meats, poultry and eggs. The fact that all vegetables must be cooked leads to serious vitamin losses. The problem of China's food supply will have to be met from a study of various sections of the country for each has its special aspects. Three of the food areas are under

Japanese control and six are free. The diets in all sections are bulky, with cereals and legumes supplying from 81 to 95 per cent of the total calories. Milk and dairy products are almost absent, the intake of animal products is very low, soybeans play a very minor role, not many vegetables are obtainable, and fruits and sugar are present in scarcely noticeable amounts. The bulk of the diet is composed of cereals. Calcium consumption is low. The calcium phosphorus ratio is from 1.4 to 1.6. In some districts of Yunnan iodine is scarce and simple goiter affects 25 per cent of the population. The plight of the generally poor nutritional situation is borne and evidenced by pregnant and nursing mothers, growing children, convalescents, and wounded soldiers. The food problems will increase as the Japanese are forced out, for they will destroy all crops as they retire. China needs increased production of leafy vegetables and fruits most suited to the specific areas, increased production of soybeans, soybean milk, curd and sprouts, improvement in animal husbandry to furnish milk, eggs and meat. Calcium may be added artificially to foods. The rural ponds should be stocked with fish to supply Vitamins A and D. Yeast should be produced as a food. Potassium iodide should be added to the table salt in goitrogenous areas. Law should forbid the sale of highly polished rice. Each major area should have its own nutritional research center well staffed by competent men capable of teaching the people better eating habits. From America, China needs now air shipments of fish liver oil concentrates, Vitamin B-complex and ascorbic acid for use in hospitals. Powdered whole milk should be sent in as soon as the Burma Road is opened. Also dehydrated pork and other meats should be sent as soon as possible (from an original report by James Claude Thomson, Professor of Chemistry, University of Nanking, Chengtu, China).

Human Amino Acid Requirements Nitrogen balance cannot be maintained in man unless the diet contains lysine and tryptophane, and normal spermatogenesis depends upon the presence in the diet of arginine. Characteristic of lysine deficiency is increased excretion of non-ketone organic acids and symptoms of nausea, dizziness and hypersensitivity to metallic sounds. Since similar excretion of organic acids occur in pneumonia, nephrosis, malnutrition, post-operative acidosis, premature infants and in rickets, it is possible that in such states, there may be an abnormality of lysine catabolism. It has been found now that methionine also is essential to the preservation of nitrogen balance, and the same importance must be attached also to the amino acid valine. Histadine, while essential to the rat, is not essential to man, but threonine, leucine, isoleucine and phenylalanine are essential. (*J Biol Chem*, 148:457, 1943).

A New Method for Vitamin Determination For this new method consult the article by Roe and Kuether (*J Biol Chem*, 149:399, 1943). It is said to be very accurate and to apply to blood and urine.

Growth Factors in Injured Cells The rapid growth and proliferation of cells at the site of an injury has long attracted attention and several investigations have indicated the release of growth or proliferation stimulating materials from the injured cells. A recent experiment in which yeast cells were injured by being subjected to sublethal doses of ultra-violet radiation showed that slightly damaged cells elaborate factors which increase all permeability, cause diffusion of nonprotein substances through cell membranes and synthesize within the living injured cells a variety of nonprotein growth stimulating substances. It is possible that the products of inflammation may contain some of the healing, growth promoting principles. Whether the factors of (Vitamin B-complex or certain amino-acids are of greatest importance is not settled but probably certain specific combinations of some of both are responsible. (*Biochem J*, 36:737, 1942).

B-vitamin Deficiency and Therapeutics By a new and simplified method of examining the urine for thiamine, riboflavine and nicotinic acid, it is said to be possible to state whether or not the individual has a deficiency in these factors. Nine out of ten cases of diarrhea in children are accompanied by a thiamine deficiency. Perhaps the National Research Council's recommended daily intake of 1.5 mg of thiamine is too high, by two-thirds. (*South Med Surg*, 103:9, 1943).

The Goitrogenic Action of Calcium Salts Many experiments have been devoted by many workers to the problems of thyroid size and the iodine concentration in the thyroid under conditions in which the calcium, as well as the chloride ions in the diet, have been made to vary. Goiters often occur in lime stone areas. Increased calcium chloride and reduced iodine in the diet may cause a goitrogenic effect. Some experiments have shown, however, that high calcium intake did not affect the size of the gland or its iodine content. The feeding of calcium chloride and viosterol together does produce a goitrogenic effect. Chlorides apparently tend to cause a decrease of the amount of iodine in the gland. It is felt that while a relative iodine deficiency is the most important predisposing factor in the development of goiter, that an excess of chloride represents a second, and positive factor. (*J Nutrition*, 25:239, 1943).

Riboflavine Metabolism It has been shown that 3 micrograms of riboflavine per gram of food is an optimum amount to obtain maximum effects as judged by growth curves, length of life, reproductive cycle, concentration of hemoglobin and the weight curves of the offspring. The addition of larger amounts does not improve the results. This means 0.9 micrograms per kilogram-calorie of food is optimal, which is the same as suggested by "Recommended Daily Allowances" (0.9 mg riboflavine per 1000 calories). (*J Nutrition*, 25:153, 1943). Riboflavine hastens the regeneration of hemoglobin. The above figures apply to adults, and for young rats larger amounts are re-

quired Experiments to determine the nature of riboflavin excretion into the intestine and its absorption from different parts of the gastro-intestinal tract (J Nutrition, 25 137, 1943) showed that probably excretion is largely into the upper portion of the small gut. The biliary tract probably plays no part in riboflavin excretion. It can be absorbed by the lower part of the small gut. It is destroyed in the large bowel. A protein diet is necessary for the retention of riboflavin in the liver (J Nutrition, 25 173, 1943)

Iron and Iron Salts in Flour Enrichment Of the several iron preparations which are used to increase the iron content of bread, ferric phytate is least efficacious in bringing about hemoglobin regeneration, as judged by feeding these preparations to rats made anemic by the use of a milk diet. But sodium iron pyrophosphate and also reduced iron were efficacious. It was found that ferric phytate was poorly absorbed. The nutritive value of some foods are enriched by the iron added as a contaminant during the processing, particularly as a result of the abrasion of iron containing grinding mills. It is not the chemical constituents of food that are important but their utilization by the body. In man 15 to 30 g of reduced iron per day are required to give the same therapeutic result as is produced by 1 g of iron as iron ammonium citrate, or by 0.2 g of iron as ferrous sulfate (J Nutrition, 25 39, 1943), (Ibid, 13 573, 1937)

Thiamine in Human Milk It has been recommended that in the feeding of healthy infants and children, early supplementation with thiamine containing foods is desirable (J A M A 120 913, 1942). Evaporated milk when diluted with an equal volume of water contains on the average about as much thiamine as does boiled pasteurized milk and considerably more than average human milk. Colostrum contains practically no thiamine, and the administration of thiamine to mothers during labor and after delivery cuts down the time required for breast milk to attain sufficient levels of thiamine. Thus, what normally requires 3 or 4 weeks can be accomplished in nine days. Cow's milk contains on the average twice the concentration of thiamine that breast milk contains, and average evaporated milk is almost as high. Probably the infant's requirement of thiamine is about 0.20 mg daily (J Pediatrics 22 43, 1943). It is important that the nutritive status of the lactating mother be given consideration.

B-vitamins in Tumor Tissue A study was made of the concentrations of several of the B-vitamins in various animal and human malignant tumors and these concentrations compared with those found in corresponding normal tissues. It was found that generally speaking the values of riboflavin, niacin and pantothenic acid for tumor tissue were relatively consistent, relatively low and well within the range of values for normal tissues. It is an open question whether the observed deviations in vitamin content are in any way connected with the critical differences

between normal and tumor tissues (Cancer Research, 2-739, 1942) (Science, 96 322, 1942)

Emergency Livestock Nutrition The most serious shortage in animal feeds due to the war, is that of protein, particularly sources of animal protein such as fish meal, tankage meat scrap and dried milk. Soybeans are being produced in quantity but there is available insufficient processing equipment needed to render soybean protein suitable for livestock feeding. Carbohydrates and fats are on the decline. There is no shortage of calcium but the lack of bonemeal brings a lack of adequate phosphorus. Alfalfa production in 1942 was off and hence pasture must be used to obtain good Vitamin A. The liberal use of protein feeds is discontinued generally. Oil meals are used as a supplement to cereal grains. Possible lack of protein feeds may cause increased susceptibility to disease and the Veterinary authorities are carefully watching for this (J Am Vet Med Ass'n, 102 217, 1942)

Vitamin C and Experimental Hepatic Damage It was found that the injection of hydrazine, a rather specific hepatotoxin, produced marked liver damage in scorbutic guinea pigs, but practically no damage in pigs protected by adequate amounts of dietary ascorbic acid. The method by which protection was thus afforded was not clarified (Arch Int Med, 71 315, 1943)

Salicylic Acid Hypoprothrombinemia Hydroxycoumarin decreases prothrombin, but not until 12 hours have elapsed following its administration, thus suggesting that the effective agent in causing hypoprothrombinemia is some degradation product of coumarin. Hydroxycoumarin has been chemically degraded, yielding salicylic acid. The administration of salicylic acid to rats whose diet was low in Vitamin K produced severe hypoprothrombinemia in 20 days. It would seem that the prolonged clotting time produced by salicylic acid is due to an induced hypoprothrombinemia. Possibly when hemorrhagic manifestations occur in rheumatic fever during the administration of salicylic acid, they are due to the drug (J Biol Chem, 147 463, 1943)

Nutritional Inadequacies in Pregnancy A number of recent studies throw some light on the fact that while the mortality of infants under one year of age has been greatly lessened there is still a group in the first few weeks of life whose mortality has been uninfluenced. To improve the fate of this group, attention was devoted to the question of the diet of the pregnant and lactating woman, and it was found that those whose diets were nutritionally adequate not only endured labor better but produced babies who survived the dangerous period. Iron is one of the greatest needed supplements in pregnancy and lactation but, of course, vitamins good sources of protein, require almost equal attention. Better diet cuts down the incidence of the toxemias of pregnancy, anemias and threatened miscarriage.

Deficiency Disease in Patients with Medical Disorders In a survey made in the Charity Hospital in

New Orleans, it was found that out of 200 patients suffering from medical disorders, as many as 79 gave clinical evidence of malnutrition due to deficiency. Special attention was devoted to deficiencies in riboflavin and niacin. It may be concluded that a medical illness is therefore a factor which may be considered valuable in showing up latent deficiencies. (South Med J 36:108, 1943)

Biotin and Cancer Since biotin is present in malignant cells in higher concentration than in normal cells, it may be assumed as essential to the cellular respiration of cancer cells. In rats certain liver tumors, produced by feeding butter yellow, were found to be prevented by the use of certain diets, but the addition of biotin to the preventive diet rendered it no longer preventive. Thus the question arose as to whether the growth of neoplasms could be reduced by withholding biotin from patients suffering from cancer. Studies have been carried out on two patients with negative results, but the problem is not settled, because in these experiments there was a failure to obtain real biotin deficiency, (J A M A, 121:1261, 1943) although this had been obtained earlier in normal subjects by a similar method.

Hemoglobin and Plasma Protein Production The most recent report from Whipple's laboratory (J Exp Med, 77:375, 1943) offers much of interest to the clinician as well as to the student of protein metabolism. Using dogs from their well known anemia colony, Robschek-Robbins, Miller and Whipple fed these animals a basal diet low in protein and adequately supplemented with iron as well as vitamins. Repeated withdrawal of blood reduced the hemoglobin and plasma protein levels, and, with protein as the only apparent limiting factor, the role of various sources of protein and the value of amino acid mixtures for the production of hemoglobin and plasma protein were studied. By determining total blood volume and calculating total hemoglobin and plasma protein production, interesting observations concerning the body economy were made.

The value for hemoglobin and plasma protein production of the following was studied: dog plasma, dog hemoglobin, hemoglobin digests, beef serum digests, casein digests, a mixture of the amino acids necessary for rat growth (Rose), and cystine plus choline. All of these were utilized by the animals. In order of decreasing effectiveness for hemoglobin production they fell roughly as follows: dog plasma given intravenously, dog hemoglobin given intraperitoneally, casein digest by mouth or by vein, beef serum digests orally or intravenously, amino acid mixture given by mouth, hemoglobin digests given intravenously or orally and finally cystine plus choline given orally. For plasma protein production the order was not quite the same. In this respect dog plasma took the lead very easily but was followed by casein digests, dog hemoglobin

given intraperitoneally, beef serum digests, hemoglobin digests given intravenously, and in the lowest category the amino acid mixtures and hemoglobin digests given by mouth.

It is noteworthy that all the substances were used to a greater extent for hemoglobin production than for plasma protein replacement. However, since the quantity of hemoglobin is roughly three times the amount of plasma protein in the dog this is not altogether surprising. It is of interest that dog plasma and beef serum digests when given orally (but not when given intravenously), as well as the casein digests, promoted plasma protein production somewhat more than the other substances tested. Curiously, when cystine replaced methionine in the amino acid mixture the balance also turned somewhat more favorably to plasma protein production. These investigators also noted that the production ratio of the amino acid mixtures, when calculated according to their theoretical protein equivalent, compared favorably with the best dietary proteins.

The implications of these studies are numerous. It is evident that the plasma proteins contribute freely to hemoglobin production and that there is a ready interchange between plasma proteins and hemoglobin in both directions. A "dynamic equilibrium" exists. In the author's words, "this all adds up to a remarkable fluidity in the use of plasma protein or hemoglobin which can contribute directly to the body protein pool from which are evolved, without waste of nitrogen, the needed proteins, whether hemoglobin, plasma protein, or tissue proteins."

We have learned that it is not wise to assume that observations in one species necessarily apply to another, but the clinician should be stimulated by these studies to give more attention to the importance of protein in hemoglobin production. It will be important to determine whether it is possible to demonstrate clear benefit from the use of protein in certain types of anemia, such as has been shown to be the case in the use of iron and of highly purified liver extracts in the treatment of chronic hypochromic anemia and the nutritional macrocytic anemias, respectively. There are many forms of anemia in the treatment of which neither iron nor liver extract is of value.

What use can be made, by proper digestion, of red cells discarded in blood banks as a source of protein for hemoglobin and plasma protein formation remains to be seen. These studies contribute also to the immediate problem concerning substitutes and supplements for plasma and whole blood in the treatment of shock and of conditions in which absorption from the gastro-intestinal tract is impaired.

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Letters

July 9, 1943—New Guinea

To the Editor

I have now been for more than a year in the tropics (New Guinea) doing field medical work. Many complaints referable to the gastro-intestinal tract are seen by the Army Doctor in the tropics. Inasmuch as these frequently simulate or complicate a surgical condition within the abdomen, it is essential that the surgeon be as familiar with these conditions as the internist. Then too, any person who comes to the tropics for the first time will have some personal experience with one or more of these conditions and to know about them is a comforting satisfaction, especially for the doctor who usually thinks the worst when he himself is involved.

A few weeks after coming into the tropics many of our officers, including myself and men had periods of profound anorexia, crampy sensations throughout the abdomen, nausea and vomiting. The vomiting usually occurred during or just after finishing a meal, most marked after the noon meal. This we felt might be due to the food which although adequate, was not too palatable and was monotonous—there being e.g. "bully beef" for several consecutive days (I must say things have greatly improved recently). However, these tendencies were most noted in those men who were working hard and long hours and at the same time perspiring a great deal. The use of added salt helped in some instances, but in others when taken in tablet form seemed to immediately increase the nausea. These symptoms, as a rule, gradually disappeared during a 14 to 30 day period. Although no laboratory examinations have been available during these periods, I am inclined to think that this occurs during the period when our body is making the necessary physiological readjustments to the excess salt loss and possibly to our necessary dietary changes. It might be interesting to make studies of the blood chlorides and serum proteins in these cases. When asked what the diagnosis was I have frequently said "Tropical Dyspepsia".

Each intense period of bombing and combat has been followed in many patients with functional dyspepsia, "functional diarrhea," aggravation of the so-called irritable colon, and at the same time an increase in the number with constipation. In many of these vague abdominal aches and pains develop and the patient, and occasionally the doctor, is concerned about the possibility of appendicitis, cholecystitis or a peptic ulcer. After a period of rest, sedation, and chiefly reassurance, most of these problems are corrected. One must not overlook the fact that a few of the patients that present these functional type complaints are intolerant to atabrine or quinine used for malaria prophylaxis or may even be suffering from chronic

malaria. I have seen one instance where a patient responded rather violently to quinine and on three occasions had severe digestive upsets when given quinine therapy. He was proven to have an allergic hypersensitivity to the substance with complete relief by stopping the drug and reproduction of the condition by again administering the same.

Patients acutely ill with malaria and in certain cases of typhus fever seem to develop a condition which clinically appears to be an acute gastritis. These patients usually respond promptly to the intravenous administration of dried blood plasma and saline solution. I have mentioned in a previous letter the frequency with which patients with an acute malaria present symptoms and abdominal findings of a surgical condition within the abdomen, namely, appendicitis, cholecystitis, or peptic ulcer. One must constantly be considering these possibilities, as it has not been uncommon for an abdomen to have been explored for a surgical condition only to find that it was acute malaria.

Even though one is in the Field where all diagnostic facilities are limited and where he is dealing with a group of individuals selected for their physical fitness he should be careful lest he overlook one of the common organic diseases of the gastro-intestinal tract. Appendicitis is the most common of these but it has been my impression that to date, I have not seen as high an incidence of appendicitis in the American soldiers in these regions as one might ordinarily expect from the same individuals in civil life. Peptic ulcer has been seen and proven by roentgenologic examination in a number of instances. In one patient less than 30 years of age, a carcinomatous gastric ulcer was diagnosed. One twenty-nine year-old officer developed a common duct obstruction due to stone formation. In another a primary volvulus of the small intestine was found. An unusual number of individuals were seen at one time with a suppurative type of mesenteric lymphadenitis the etiology of which could not be determined.

At times I have had an opportunity to visit Native missions and hospitals here in Papua. In some instances I have performed operations on the Natives for such conditions as strangulated hernia (a common finding), fractures, various traumatic conditions, etc. On these occasions I have examined other Natives and inquired as to the medical problems commonly seen. Of course it is difficult to get them to visit physicians and a person of 50 is considered very old but one can obtain some fairly accurate general impressions. They rarely, if ever, have appendicitis. No cases of cholelithiasis have been seen or heard of, cancer, although

reported, is apparently very rare. I doubt that peptic ulcer exists among them. Malaria, dysentery, pulmonary conditions, and rambesia are the most prevalent diseases.

It has been interesting to compare a few of the gastro-intestinal problems seen as an Army Doctor in

the tropics to those I have been familiar with in private life. With kindest regards, I am

Sincerely,

Leonard K. Stalker, Capt. M.C., 0-475412,
1st Portable Surgical Hospital,
APO 503—P.O. San Francisco, Calif.

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M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

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CLINICAL MEDICINE STOMACH

HARRINGTON, S. W. *Roentgenologic Considerations in the Diagnosis and Treatment of Diaphragmatic Hernia.* *Am. J. Roentgenol.*, v 49, p 185, February, 1943.

Diaphragmatic hiatus hernia should be suspected in the patient who, in the 5th decade, experiences substernal distress during the night which is relieved by assuming the erect position or who experiences dysphagia with regurgitation subsequent to an illness associated with vomiting or coughing. The degree of involvement of the diaphragm and increased intrathoracic pressure determine the nature of the symptoms. Traumatic diaphragmatic hernia may be caused by an injury or inflammatory necrosis of the diaphragm. Non-diaphragmatic hernia is either congenital or acquired; in the former it is probably due to an embryonic misdevelopment. Herniation of the stomach into the posterior mediastinum is the commonest type in adults. At first only the stomach is included in the hernial sac but later on the colon, spleen and omentum may be pushed through. Treatment consists of operation under positive pressure, with retraction of the viscera into their normal position and repair of the enlarged hiatus. Roentgenographic and even bronchoscopic examinations are necessary before operation to check the diagnosis and should also be made post-operatively. Congestion and pleural effusion should be treated immediately.—M. I. Theoné

BOWEL

STANNESS, H. S. *"Spurc" Trans.* *Roy. Soc. Trop. Med. and Hyg.*, v 36, p 123, 1942.

After criticizing earlier explanations of the nature of spurc, the author offers a new theory based on the "position" hypothesis backed by evidence that unsplit neutral fats follow a different course after digestion and therefore have a role in metabolism differing from that of the fatty acids. The following points of evidence are tentatively presented. Fat deficiency is due to faulty absorption of fatty acids and cholesterol, therefore there is a secondary failure to absorb the necessary neutral fats (glycerides). Glucose

deficiency is due to absorption by diffusion and not by active selection, the same is also true for glycerol. These absorption deficiencies are due to the failure of phosphorylation, the absence of this process prevents absorption from taking place in the intestinal mucosae. If fatty acids are not absorbed then neutral fatty emulsions also are not taken in. Levulose absorption is normal even though glucose intake is inhibited. Calcium loss is due to "fixation" in the insoluble soaps in the intestines. Phosphorus loss is due to failure of phosphorylation and the consequent absences of soluble phospholipids. Unabsorbed fatty acids and glucose undergo fermentation in the intestine and cause distention. Enzyme failure, and not adrenal hormone failure, hinders the phosphorylation process and this is responsible for the condition known as spurc. These enzymes are probably connected with the vitamin B members (riboflavin, niacin, pyridoxin, and (?) choline). The desaturation of the fatty acids at the time of lecithin formation in the intestinal mucosa may be due to the failure of pyridoxin activity. The kinds of fatty acids present may be important, probably all do not react alike in any given set of conditions. The anemia of spurc (and other nutritive anemias) may be due to the loss of lecithin. There are no pathological changes in spurc—only a defect in phosphorylation and therefore spurc is properly regarded as a disease of malnutrition.—Courtesy Biological Abstracts

SILVERMAN, D. N. AND FRIEDRICH, A. V. *Increasing Incidence and Complications of Chronic Bacillary Dysentery.* *New Orleans Med. Surg. J.*, v 95, p 401, March, 1943.

The incidence of bacillary dysentery has increased in recent years. As compared with former years, Shiga and Flexner organisms are more common while lactose-fermenting organisms are less common. The danger of spread of the infection from camps to local communities by soldiers on leave and the introduction of the infection into camps by new arrivals is very great. Isolation of each suspected case is essential if the spread of the disease is to be prevented.—D. A. Wocher

WILSON, H. *Diagnosis and Treatment of Carcinoma of the Colon* *Tenn State Med. Ass J*, 1 36, p 47, February 1943

The author discusses the symptomatology of cancer of the colon and the relation of the symptoms to the anatomy and physiology to the different areas of the colon. Carcinoma of the right colon usually results in mild digestive disturbances, anemia, and altered bowel habits while blood in the stool is not common. Obstructive symptoms, whether acute or chronic usually occur with carcinoma of the left colon and blood in the stool is common. Diagnosis should be based on history, chemical analysis of stool, proctoscopy, x-ray findings. Treatment depends on the individual case.—G Klenner

GUILD, WM A. *Anal Fistula* *J. Am Inst Homoeopathy*, v 35, p 343, 1942

Anal pathology is of more than local significance. Anal fistula differ widely from deeper rectal fistulae and arise from depressions at the anal-rectal junction rarely above. Extension of an eroded pocket in the anus is favored by pressure of the stools and the milking action of peristalsis. Complete excision is the treatment of choice.—Courtesy Biological Abstracts

LIVER AND GALLBLADDER

TAB, R J., GREENWALT, T J., AND DAMASHEK, W. *Output of Bile Pigment by Newborn Infants and by Older Infants and Children* *Am J Dis Child* v 65 p 558, April 1943

This study was undertaken in an attempt to derive some figures which could be used to determine the normal output of bile pigment in the child. An historical survey is made of the work which has been accomplished on bilirubin and the urobilinogen and urobilin in both feces and urine, mentioning various methods of determination. In their own work the authors collected the stools from 30 normal newborn infants and found the average per diem fecal bilirubin for 1-5 days was 8.6 mg, for 5-10 days, 5.7 mg, and for 10-15 days 5.3 mg. In the corresponding periods the fecal urobilinogen ranged from a trace to 0.70 mg per day. The hemolytic indexes for 8 of these infants between the 5th and 11th days ranged from 0.5 to 29.7. A study of six infants was made to discover the age at which bilirubin disappears from the stool but since it was still present in small amounts in 4 of them at the end of 54, 64, 65, and 75 days respectively (although without consistency in any one), no accurate statement could be made. Fecal urobilinogen was found to be below 2.5 mg per day in children prior to 2 years of age, while from 3 to 11 years the range was 2 to 7 mg per day (50 to 100 mg daily in average adult) based on children convalescing from illness uncomplicated by hemolytic, hepatic or biliary conditions. In children (4 cases) with a high hemolytic index, the fecal urobilinogen was definitely increased, but after splenectomy a definite fall in both the fecal urobilinogen and the hemolytic index occurred.—Wm. D. Beamer

CHRISTOPHER F., BENJAMIN, E. L. AND GAWDY F. K. *Infarction of the Gall Bladder* *Surgery*, Vol 13, p 444, March, 1943

A clinical diagnosis of acute cholecystitis in a 59

year-old woman proved at operation to be one of hemorrhagic infarction of the gall bladder. Cases of gangrene of the gall bladder without infection and due to infarction are uncommon. The cause of the infarction in the present instance could not be determined. No signs of ulceration or infection were present.—M I Theone

EDWARDS L. R. L. *An Outbreak of Epidemic Catarrhal Jaundice* *British Med J* p 474, April 17, 1943

This outbreak occurred in an urban area while all previous outbreaks have been in rural areas. It included 64 cases (figures estimated to report 80% of the cases) among school children and young school-teachers. The epidemic began in the spring and continued over the summer, with several schools being involved. The incubation period is estimated at 3 to 4 weeks. Vomiting occurs during the prodromal period and may last from a few days to a week. This has been attributed to a duodenitis. With the cessation of vomiting jaundice appears first in the cornea, and then in the course of a few days spreads to the skin of the face, trunk, arms and lower limbs. The jaundice lasts from a few days to 2 weeks. There was a well-marked leukopenia with a relative lymphocytosis. The disease is spread by an ultramicroscopic virus of the upper respiratory tract and close personal contact is necessary. The infective period is short and 2 weeks isolation seems sufficient.—G P Blundell

GARVIN, C F. *Cardiac Cirrhosis* *Am J Med Sci*, Vol 205, p 515 April 1943

Thirty-five instances of cardiac cirrhosis were encountered in a series of 790 cases coming to post-mortem with a final diagnosis of heart disease. Those cases not dying with congestive failure were excluded from this study. The diagnosis of cardiac cirrhosis was only made when there was sufficient fibrosis to produce architectural distortion in the liver. Cardiac cirrhosis was encountered in 11.8% of the cases dying with rheumatic heart disease, in 5.3% with hypertensive heart disease and in only 1.7% of the remaining cases. Almost 1/3 of the cases with tricuspid stenosis showed this lesion at post-mortem. The diagnosis was made ante-mortem in only five of the above cases and the author points out that this is a difficult diagnosis to make clinically. However, it occurred most commonly in patients who had undergone repeated episodes of failure, was commonly associated with splenomegaly of a moderate degree, and was associated with a greater incidence of ascites than was the group not complicated by this condition.—L J Pincus

ULCER

TIMONEY, F X. *Perforated Peptic Ulcer* *Ann. Surg*, Vol 117, p 710 1943

The author concludes that "implantation of powdered sulfanilamide in the peritoneal cavity and in the wound is indicated in the treatment of perforated peptic ulcer. It is an effective agent in reducing mortality and lessening the occurrence of post-operative infection of wounds."

This conclusion is based on observations on 254

Value of Proctoscopy in the Diagnosis of Amebiasis

B3

RAYMOND I JACKMAN, MD*

and

WILFORD L COOPER, MD†

ROCHESTER, MINN.

AMEBIC dysentery, at one time considered a tropical disease, is now considered a nearly universal type of infection, and it will probably become much more so with the return of our soldiers after the war. It has been variously estimated that from 5 to 10 per cent of the population of the United States harbor the parasite.

DIAGNOSIS

The absolute diagnosis of amebiasis is accomplished only when *Endamoeba histolytica* has been identified in the stools, tissues or bodily discharges. Because of the possible presence of at least four other species of amebae and several other protozoa identification of *Endamoeba histolytica* may be very difficult. Fairly commonly examination of the rectal discharges will not be sufficient to identify the parasite. Therefore advantage of all diagnostic procedures applicable should be considered. The value of proctoscopy in the diagnosis of amebic dysentery is considered by many as being controversial. With this in mind we set out to answer for ourselves the following questions:

1. What percentage of patients who were found to have *Endamoeba histolytica* by examination of stools were found to have ulceration of the lower part of the bowel typical or suggestive of amebic ulcers?

2. In how many cases did patients have typical or suggestive ulceration on proctoscopy but repeated examinations of stools gave negative results and the diagnosis was afforded by swabs or scrapings from the ulcers?

3. How frequently do anal inflammatory lesions such as anal abscesses and fistulas occur in amebic dysentery?

4. What other lower intestine findings occur in amebic dysentery?

To answer these questions we studied the records of 115 patients who were proved to have amebic dysentery.

Question 1. What percentage of patients who were found to have Endamoeba histolytica by examination of stools were found to have ulceration of the lower part of the bowel by proctoscopy?—Manson-Bahr¹ stated that in 258 cases in which sigmoidoscopy was done, amebic ulcers and other characteristic lesions were found in 234 (90 per cent). In twenty-four (9.3 per cent) of the 258 cases, the mucosa of the lower part of the bowel had a normal appearance. He con-

cluded that routine sigmoidoscopy has proved its value as a means of securing a positive diagnosis.

In our study of 115 cases, we did not make any attempt to segregate them into acute or chronic phases of amebic colitis. All of the patients had sufficient symptoms referable to the lower part of the bowel to warrant examinations of stools, as well as sigmoidoscopy and roentgenoscopic examination of the colon.

In twenty-four (20.8 per cent) of the 115 cases there was ulceration of the lower part of the bowel typical or suggestive of amebic ulceration. It must be remembered that the type of amebiasis observed at the Mayo Clinic is somewhat different from the type observed in other sections of the country in that in most of the cases the condition is of long standing and has been treated. This explains the relatively low percentage of gross ulceration noted.

As to the location of the ulcers it did not seem to us that there was any predilection for the edges of the valves as is suggested frequently by other writers on the subject.

Question 2. In how many cases did patients have typical or suggestive ulceration in the lower part of the bowel but repeated examinations of stools gave negative results and the diagnosis was afforded by swabs or scrapings from the ulcers?—Of the 115 cases studied, we found two (1.7 per cent) which fell into this category, that is repeated examinations of stools gave negative results, but scrapings from rectal ulceration in one case and biopsy of an ulcer in the other case afforded the means by which *Endamoeba histolytica* was found. In seventy-seven of Manson-Bahr's 258 cases in which there was ulceration of the lower part of the bowel, examination of stools gave negative results and the active amebae were recognized only in scrapings from the ulcers. Rodaniche and Palmer² reported one case in which the patient had typical rectal ulcers and in which repeated examinations of the fecal mass gave negative results but repeated proctoscopic swabs were positive. It would therefore seem that one is justified in making the following definite statement: Given a patient suspected of amebiasis and examinations of whose stools give negative results, direct examination of the bowel by means of proctoscopy should be undertaken with the idea of obtaining positive evidence from the ulceration.

Question 3. How frequently do anal inflammatory lesions such as anal abscesses and fistulas occur in amebic dysentery?—One of us (Jackman) and Smith^{3,4} have pointed out previously the relative frequency with

*Section on Proctology, Mayo Clinic.
†Fellow in Proctology, Mayo Foundation.
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which anal abscess and fistula occur in chronic ulcerative colitis and regional ileitis. We have not found this to be true in amebic colitis. One of the 115 patients had an ischio-anal abscess and one had an anal fistula. This incidence of 17 per cent is in striking contrast to an incidence of the same condition in more than 30 per cent of cases of regional ileitis in a similar study and an incidence of 84 per cent in cases of chronic ulcerative colitis.

Question 4 What other lesions of the lower part of the bowel were observed in association with, or as a complication of amebiasis as determined by sigmoidoscopy? — One of the 115 patients had an amebic granuloma in the lower part of the sigmoid. The clinical significance of this lesion lies in the fact that it may be confused easily with other tumefactive lesions particularly malignant lesions. Differential diagnosis was made in this particular case by finding the parasite in the stool and by histologic study of specimens removed at the time of proctoscopy.

However, finding of *Endamoeba histolytica* in the stool alone is not sufficient to rule out a malignant growth, as indicated by two of the patients, who were found to have the parasite by examination of stools but who on proctoscopy were found to have an adenocarcinoma in the region of the rectosigmoid. This further emphasizes the importance of proctoscopy, even though the parasite has been found in the stool. One of these patients in whom the carcinoma was not palpable by digital examination received vigorous treatment with amebicides and, on failure of symptoms to disappear, was then sent for proctoscopic examination, at which time the carcinoma was discovered in the lower part of the sigmoid.

Two patients were found to have single sessile polyps in the sigmoid. It is possible that these polyps, or as some authors describe them, pseudopolyps, are similar in their formation to the polyps which occur

in chronic ulcerative colitis. The polyps were destroyed easily by fulguration.

Rectal stricture was found in one of the 115 cases of amebic dysentery. The patient gave a history of having had the disease for many years. The stricture did not resolve after intensive treatment. Two of the group had scarred contractions of the anus.

SUMMARY

A study of 115 consecutive patients who had amebic dysentery was carried out for the purpose of determining how much value proctoscopy has in the diagnosis of the condition.

Ulceration of the lower part of the bowel, suggestive of amebiasis, as determined by proctoscopy, was found in 20.8 per cent of the cases of amebic dysentery.

Biopsy and scrapings from the ulcers at the time of proctoscopy afforded the diagnosis in two cases in which repeated examinations of stools had given negative results.

In comparison with the other infectious types of diarrhea, anal abscess and anal fistula were not common complications.

The occasional coexistence of a carcinoma or other tumefactive lesion with amebic dysentery is sufficiently frequent to warrant proctoscopy in every case in which amebic dysentery is suspected.

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Pathogenicity of Intestinal Protozoa

By

HORACE WENDELL SOPER, M.D. F.A.C.P.

SAINT LOUIS, MISSOURI

NEARLY all the Parasitologists believe that Intestinal Protozoa are not pathogenic. This view was held by the old school of German Gastro-enterologists. Craig and Faust¹ express the same opinion, but state that they find the parasites only in cases of diarrhea.

Kofoid (2) emphasizes the relative importance of the Hematozoan group such as trypanosomiasis, leishmaniasis, malaria, etc., in their more severe pathogenic qualities to the host. He believes, however, that the flagellate parasites of the intestine, particularly *trichomonas hominis*, have real tissue invasion capabilities. He states that there is abundant clinical evidence that

they may become pathogenic when the resistance of the host has been impaired by infection. He cites Hinkelmann (3) who reports that 5 c.c. of blood from a human case of diarrhoea and intermittent fever, mixed with distilled water and centrifuged, revealed the presence of *trichomonas intestinalis*, also Ratz (4) found *trichomonas* in the liver of pigeons. These flagellates have been found in pleural transudates and lesions of the mouth, jaws, tonsils, esophagus and stomach.

My own clinical experience has established the pathogenicity of the flagellates. For many years I have insisted that every patient who enters the clinic for examination submit a specimen of the feces for labora-

tory analysis; as a result, many cases of flagellate infestation have been disclosed. The majority of such patients exhibited no symptoms that could be attributed to them, however, others gave evidence of disturbances which were produced by infestation of flagellates, particularly *Trichomonas*, *Chlamastix mesneli* and *Endamoeba coli*, as etiologic factors in the production of the clinical picture of *Chronic Catarrhal Enteritis*. The patient complains of bowel irregularity, diarrhoea with intervals of constipation, excess intestinal gas, etc. The feces analysis reveals excess of mucous, particularly the microscopic small clumps or islands enclosing leucocytes, as well as undigested starch granules and striated muscle fibres, in the more severe cases, a one to two plus occult blood reaction was secured (Guaiac test). I found that one stovarsol .25 gm tablet three times daily before meals for six days to be specific in eradicating all the flagellates excepting the *Giardia enterica*, there is no question about the pathogenicity of this parasite which is now easily removed by Atabrine, which was discovered to be a specific by Galli-Valerio (5).



Fig No 1 Acute jejunitis much dilated, ending abruptly at the ligament of Treitz

A very interesting case came under my care in 1936 which I presented in my book on Clinical Gastroenterology*. It may be briefly summarized as follows. Male, aged fifty-two, developed prostatic symptoms and was subjected to massage and cystoscopy which was followed by chill and fever which persisted for one week when I saw him in consultation. X-ray film of the stomach revealed a large dilated duodenum and jejunum. Feces strong occult blood reaction and many trichomonas. He vomited blood and had severe epigastric pain. Operation was performed and a large distended jejunum in the stage of acute inflammation was disclosed. No tumor mass or obstructive agent could be located. The incision was closed. He was given the stovarsol treatment, and made a quick uneventful recovery. Subsequent x-ray films some months later exhibited normal appearing duodenum and jejunum. He has been checked annually since

and remains in excellent health with no trichomonas in the feces (Fig No 1).

Regional enteritis may involve any segment of the small intestine. The terminal ileum is the most frequent site and has been found in the acute stage simulating appendicitis. The chronic form characterized by a narrowing of the lumen, and thickening of the wall by a condition which the pathologists term a "primary non-specific granuloma".

A case which came under my observation on April 1, 1940, was a child aged ten years who had suffered from bronchitis subacute in character for a period of six weeks. For the past week she had developed fever "gas pains" in the lower abdomen, and constipation. Feces analysis, soft, mushy in character, no visible mucous. Four plus occult blood reaction (Guaiac test). Microscopically many endamoeba coli and small clumps of mucous enclosing leucocytes. Blood showed usual picture of secondary anaemia. Urinalysis, nothing abnormal. X-ray disclosed dilated terminal ileum (Figs No 2 and No 3). She received 125 gm stovarsol for six days. The fever subsided and occult blood reaction and parasites were absent from the stool on the 7th day. An X-ray barium enema was given under pressure April 11th, and a normal



Fig No 2 Note dilated terminal ileum 24 hours after barium meal

pattern of the terminal ileum was obtained. She was seen again May 3rd and serial films of the small intestines following oral barium revealed normal small intestinal pattern including terminal ileum. Her blood was now normal and her general condition excellent.

But few case reports of acute jejunitis appear in the

literature J N Hall reported a case in an infant aged eleven months that came to autopsy. Several cases involving the duodenum and jejunum have been reported recently.

A case of megaduodenum and megajejunum by P W Brown and J deJ Pemberton (7) of the Mayo Clinic came to operation with excellent results. The films they display are very similar to the one I presented in my case of acute jejunitis.



Fig No 3 Terminal ileum after barium enema given under pressure.

Walter R. Johnson (8) reported a case of chronic non-specific jejunitis with unusual features. The entire involved area was resected and the specimen microscopically revealed the same type of tissue reaction

which has been described by Crohn (9) in his work on regional enteritis.

Three other patients since that time presented symptoms of acute regional ileitis following influenza, fever, pain in the right iliac region and strong occult blood reaction in the feces, which were "swarming" with trichomonas intestinalis. They all made good response to stovarsol therapy.

It is curious to note that no flagellates were found in the chronic cases of ileitis that came under my observation; they evidently disappear after the acute stage has ceased.

CONCLUSION

1 Intestinal protozoa are pathogenic, producing a low grade chronic enteritis which is often not diagnosed.

2 In some cases they become activated by some infectious agent attacking the host, and attain a degree of pathogenicity which results in a regional ileitis which may occur in any segment of the small intestine. This acute stage is amenable to specific treatment by Stovarsol.

3 If the ileitis advances to the chronic stage surgical intervention is indicated.

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The Value of the Cough Sign in Acute Appendicitis

By

S BEN ASHUR MD

JERSEY CITY N J

THE typical case of acute appendicitis is readily recognized by the general practitioner. Very often, however, the disease will tax the skill of the most able clinician. In many cases the classical symptoms are

absent or come late in the disease. One can recall instances of acute appendicitis with little or no signs and conversely other diseases with signs and symptoms simulating acute appendicitis.

Since the days of Fitz, nausea, vomiting, pain, tenderness and spasm have been regarded as the cardinal

features of acute appendicitis. Of these, spasm is the most significant sign. Its evaluation, however, is very often difficult early in the disease.

For many years I have utilized the cough sign in the examination of acute abdominal cases, and have found it of great value in the differential diagnosis, and almost pathognomonic of acute appendicitis. In eliciting the sign the examiner places the tips of his fingers under the left costal margin in the region of the spleen. The patient is then asked to take a deep breath, exhale completely, and then cough. When positive, the patient will point to the area of the suspected appendix as the site of severe pain. This sign is rarely mentioned in text books on medicine nor is it emphasized in the voluminous literature on this disease.

In order to secure factual evidence of the value of this sign to replace the clinical impression a study was made of 400 cases of acute abdominal diseases admitted to the Greenville Hospital between the years of 1938 and 1942. The records were studied with certain points of the history, physical examination and laboratory data in mind. These included the presence or absence of vomiting, localized or generalized pain, the presence or absence of rebound tenderness, spasm, cough sign, fever and leucocytosis.

For the purpose of this study, the cases were divided into two groups. The first included cases in which acute appendicitis was found at the operation and confirmed by the pathologist. Only those with uncomplicated acute appendicitis were included in this study. Cases with rupture, abscess formation, and peritonitis were excluded. The second group comprised cases with non-appendicial diseases. These two groups are listed in Table I. The second group was again subdivided into cases with acute abdominal diseases other than acute appendicitis, and those simulating acute abdominal diseases. This latter group included cases which were not operated on because they subsequently presented sufficient clinical and laboratory evidence to

and 202 had non-appendicial disease. Of this latter group, 106 had non-appendicial acute abdominal disease and 96 cases simulated acute abdominal diseases. The results are shown in the following tables and are best described with reference to each of the signs and symptoms studied.

ANALYSIS

Localization of Pain

In 79.3 percent of the cases with acute appendicitis the pain was localized to the right lower quadrant of the abdomen and in 20.2 percent, the pain was diffuse. In 80 percent of those in whom the pain was localized to the right lower quadrant the pain began in the region of the umbilicus or generalized all over the abdomen. Of the non-appendicial cases, 65.3 percent had the pain localized to a definite area of the abdomen and 34.6 percent had the pain generalized.

Vomiting

Vomiting occurred more often in non-appendicial disease—in 56 percent as compared with 40.4 percent in acute appendicitis. It was present more than twice as often in non-appendicial acute abdominal diseases—in 75.5 percent as compared with 34.4 percent in those simulating an acute abdomen.

Rebound Tenderness

Rebound tenderness occurred in 81.8 percent of the cases with acute appendicitis and in 70.8 percent of the non-appendicial cases. It was present in 75.5 percent of the non-appendicial acute abdominal diseases and in 65.6 percent of those simulating acute abdominal diseases.

Spasm

This sign was present in 64.6 percent of the cases with acute appendicitis as compared with 38.1 percent of the non-appendicial series. It is to be noted that it was present twice as often—in 49 percent—of the cases with non-appendicial abdominal diseases as compared with 26.1 percent of those simulating acute abdominal disease.

Cough Sign

The cough sign occurred almost three times as often—in 70.7 percent of the cases with acute appendicitis—as compared with 24.2 percent of the non-appendicial group. It was present more often in 36.8 percent of the non-appendicial acute abdominal diseases—as compared with 10.1 percent of those simulating an acute abdomen.

Fever

Fever was present almost equally in acute appendicitis (60.1 per cent) and in non-appendicial cases (51.5 percent). Leucocytosis, however, occurred more often in acute appendicitis (76.7 percent) than in non-appendicial cases (57.9 percent).

COMMENT

Murphy has emphasized the order in which symptoms appear in acute appendicitis. Pain precedes nausea and vomiting, elevated temperature and abdominal tenderness. If vomiting precedes pain, the con-

TABLE I

Symptoms and Signs	Acute Appendicitis 198 Cases		Non Appendicial Diseases 202 Cases	
	No. of Cases	%	No. of Cases	%
Vomiting	80	40.4	113	56
Localized pain	157	79.3	132	65.3
Generalized pain	41	20.2	70	34.6
Rebound tenderness	162	81.8	143	70.8
Spasm	128	64.6	77	38.1
Cough sign	140	70.7	49	24.2
Fever	119	60.1	104	51.5
Leucocytosis	152	76.7	117	57.9

change the original impression of an acute abdomen. These two subdivisions are tabulated in Tables I and II respectively.

Of the 400 cases studied, 198 had acute appendicitis

dition is probably not appendicitis. There are a few interesting facts that can be noted in this study. Vomiting occurred more often in non-appendicial diseases than in acute appendicitis. Also, the incidence of rebound tenderness was high in all three groups and

CONCLUSION

In a series of 400 cases admitted for acute abdominal diseases, the cough sign was found almost pathognomonic of acute appendicitis, occurring three times as often as in non-appendicial diseases.

TABLE II
Non-appendicial Acute Abdominal Diseases

Diagnosis	No of Cases	Symptoms and Signs							
		Vomiting	Localized Pain	Generalized Pain	Rebound Tenderness	Spasm	Cough Sign	Fever	Leucocytosis
Acute Cholecystitis	26	11	19	7	21	15	4	20	23
Intestinal Obstruction	18	18	2	16	5	0	0	2	-
Ruptured Peptic Ulcer	17	14	15	2	17	1	16	15	1
Ruptured Ectopic Pregnancy	21	16	18	3	13	2	3	6	12
Ruptured Luteal Cyst	11	8	6	5	11	9	-	9	10
Acute Pancreatitis	6	6	2	4	6	6	6	6	6
Torsion of Ovarian Cyst	2	2	1	1	2	1	1	2	2
Mesenteric Thrombosis	3	3	1	2	3	0	0	3	3
Pneumococcal Peritonitis	2	2	0	2	2	2	2	2	2
Total	106	80	64	42	80	52	39	77	81
%		75.5%	60.4%	39.7%	75.5%	49.0%	36.8%	61.2%	76.4%

TABLE III
Cases Simulating Acute Abdominal Disease

Diagnosis	No of Cases	Symptoms and Signs							
		Vomiting	Localized Pain	Generalized Pain	Rebound Tenderness	Spasm	Cough Sign	Fever	Leucocytosis
Gall Stone Colic	27	15	21	6	1	4	2	0	0
Acute Salpingitis	21	3	18	3	18	11	5	19	19
Renal Colic	19	3	15	4	11	3	0	0	0
Gastro Enteritis	14	5	5	9	9	0	0	9	6
Pneumonia	5	2	3	2	3	2	3	5	5
Renal Infarction	3	2	2	1	2	2	0	3	3
Regional Ileitis	4	1	3	1	3	-	0	3	3
Coronary Thrombosis	3	2	1	2	0	1	0	0	0
Total	96	33	68	28	63	25	12	39	36
%		34.4%	70.8%	29.2%	65.6%	26.1%	10.1%	40.6%	37.5%

occurred somewhat more often in acute appendicitis. Similarly, spasm occurred slightly more often in acute appendicitis than in the other two groups. The cough sign was present almost three times more often in acute appendicitis than in non-appendicial diseases.

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A Plan of Treatment For Diabetic Acidosis*

By

DANIEL P FOSTER, M D

WM L LOWRIE M D

and

JAMES MAC MILLAN, M D

DETROIT MICH

THE time, early 1922, the place, The Massachusetts General Hospital, one of the actors, a comatose patient breathing rapidly through parched, cherry red lips. The fruity odor of acetone tinted the air. Around the bed stood a group of expectant residents and house officers. One of these approached the patient, syringe in hand, in which was 8 units of the newly discovered hormone, insulin. The dose was administered only after emergency measures for the treatment of hypoglycemia were made available. Other therapeutic agents for the treatment of diabetic acidosis, namely subcutaneous fluids and salt and intravenous glucose, were administered. The patient was attended constantly day and night by physicians who noted carefully the change incident to recovery from this diabetic accident, previously, so uniformly fatal. Neither we, nor anyone else knew what the result would be. The result the patient recovered. The joyful news traveled fast, and in two weeks a total of thirteen diabetics in acidosis were admitted to the hospital. All survived. These patients previously had been considered beyond hope and left in their homes to die.

Since that time, studies by hundreds have been made to determine the most efficient method of using insulin, fluids, salt, and glucose to combat diabetic acidosis. These medicaments, in proper combination and amount constitute the basic ground work for a successful outcome.

Plans of successful management vary widely and need modifications based on the changing condition of the patient, the length of time he has been in acidosis, its severity, and his hour to hour response to therapy. The variations from the basic plan depend upon clinical judgment, and observation, and the results of chemical analyses of the blood and urine.

Team work, of the highest order by physician, nurse, and laboratory worker is demanded for success. The emergency calls for a medical operation of great complexity. This paper is devoted to the technique of the management of diabetic acidosis or coma, and presents a method of recording immediately the invaluable data which will permit the timely application of the proper medical aid as indexed by the progress of the patient.

As rapid recovery from acidosis as is possible is desirable, because the mortality rate seems to have a

relationship to its duration. The longer the acidosis exists the more likely is the patient to succumb. There is also mortality relationship to the severity of the acidosis. Before the days of insulin, few patients recovered whose blood carbon dioxide combining power was less than 20%. This figure is now changed and there are many records of recovery with the carbon dioxide combining power of the blood below 10%.

The treatment of diabetic coma requires hospitalization as much as do surgical emergencies. Many times it is a surgical emergency, of an acute infectious nature, which has unbalanced a previously well controlled diabetes and permitted an incomplete burning of fats. Surgery is successful in a diabetic only when the acidosis has been corrected and the blood sugar brought under reasonable control.

The object of therapy in most metabolic disease, including acidosis, is to re-establish normal quantitative values for the chemically altered body fluids. Normal cell function is possible only when the normal concentration of body salts is maintained. These consist in both organic and inorganic materials and many of these are profoundly altered in diabetic acidosis. Further, abnormal metabolites, such as ketones, accumulate, and must be gotten rid of either through oxidation or excretion. If diarrhea and vomiting are associated with diabetic acidosis they occasion further loss of fluids and valuable ions. Atchley et al (1) made a beautiful detailed study of electrolyte balances in diabetic acidosis and the results of their study made possible a more logical approach to treatment.

All procedures which one carries out in treatment are based on an attempt to correct the pathological physiology created by the acidosis. Re-establishment of carbohydrate oxidation is one of the essential factors in recovery, for it is well known that ketones are completely oxidized to carbon dioxide and water only when there is glucose and insulin available in quantities sufficient to permit its proper utilization. This chemical reaction is expedited by a normal body temperature and is doubtless interfered with when the circulation is inadequate. Thus, there is definite indication for restoring the normal temperature and blood pressure. It may be wise at times to supply artificial heat in the form of warm blankets. Support of the circulation with caffeine and an adequate amount of fluid is absolutely essential.

The above measures contribute to the maintenance

*Division of Metabolism Department of Medicine Henry Ford Hospital.
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or re-establishment of normal renal function which is a very substantial aid to the correction of acidosis. The ammonia formed in the kidney neutralizes its quota of acids and the excretion of acid ions by this route is extremely important. It constitutes the major mechanism for the elimination of inorganic salts. Anuria, in the diabetic in acidosis, is always looked upon as having grave prognostic import.

There is some justification for the differences of opinion regarding the advisability of administering carbohydrate early in the treatment of acidosis. The blood sugar is usually high and it seems illogical to add more carbohydrate to the already abnormal sugar content. It is probably true the presence of high blood sugar interferes with glucose utilization and that a reasonable control should be established before the burden of more carbohydrate be imposed. On the other hand, hypoglycemia is definitely to be avoided and of the two abnormal conditions, hypoglycemia is the least desirable.

In the dehydrated state, there may be a relatively higher blood sugar reading than the total content of glucose in the body would cause, if dehydration were not a factor. Probably the best practice is a compromise, and when there is chemical evidence of a decreasing blood sugar, carbohydrates should be administered, by some route, at regular two hour intervals. If the blood sugar level reached is below 150 and large quantities of insulin have already been administered no other route than the intravenous should be relied upon, in order to insure the presence of glucose in the blood stream to balance its effect.

It has been stated that salt fluids, glucose and insulin are the four horsemen in the treatment of diabetic acidosis but the greatest of these is fluids. These should be administered by every possible route, by mouth if the patient is not vomiting, by rectum intravenously, and by hypodermoclysis. During the first 24 hours most patients absorb and utilize with benefit 5,000 or even 8,000 cc of fluid. Normal saline intravenously and under the skin is essential because of the abnormal loss of salt and water during the development of acidosis. Water without salt will leave the body more quickly than water with salt and the correction of dehydration will be delayed if salt is not provided. During the development of acidosis sodium and chloride and water balances all become markedly negative.

It is very likely that the diabetic in acidosis is temporarily a total diabetic. The function of the islands of Langerhans seemed to be completely arrested during the acidosis period of Atchley's (1) patient T M. Further, if the circulation is inadequate, subcutaneous insulin may be dormant or be absorbed very slowly. This fact contributes logic for the occasional administration of intravenous insulin. When a favorable response to treatment is not apparent rather promptly the intravenous route for insulin should be resorted to.

The intensive schedule for combating acidosis should not be discarded too soon, but rather, relinquished gradually by decreasing the dose of insulin and lengthening the intervals of insulin administration as signs of

recovery appear. Gradually, also, the glucose to balance the insulin should be less in quantity and administered less frequently. Many patients have had relapses because it has been assumed too early that an adequate balance had been re-established.

When a regular diet is resumed a high carbohydrate (200 gms) allowance should be provided including only foods easily digested and bland in nature. As soon as the gastro-intestinal tract will tolerate food it should be prescribed and the intravenous glucose diminished proportionately.

Initial Orders

The initial orders for the treatment of the diabetic in acidosis might be tabulated as follows:

- 1 Absolute bed rest. Avoid exposing patient.
- 2 Record temperature (rectal) pulse, and respiration every hour.
- 3 If temperature is subnormal, surround patient with warmed blanket. (These are to be discontinued when temperature reaches 98 degrees Fahrenheit.)
- 4 Warm saline enema. (Do a rectal examination at this time to rule out a fecal impaction.)
- 5 Wash stomach with warm bicarbonate solution in selected cases, e. g. patients with persistent vomiting or other gastric complaints.
- 6 Record blood pressure every hour. Administer caffeine sodium benzoate, grains $7\frac{1}{2}$, every half hour for blood pressures below 100 systolic. If blood pressure does not respond administer normal salt solution intravenously. Transfuse with whole blood or plasma if patient is in severe shock.
- 7 Obtain urine at once. Catheterize if necessary. If patient is in coma, insert indwelling catheter. Examine urine for volume, sugar and diacetic acid every hour. Also examine urine routinely daily. Be certain bladder is completely emptied every hour.
- 8 Obtain blood and examine for sugar, CO₂, N P N, chlorides and cholesterol. Determine blood group. Repeat blood sugar CO₂ at eight hour intervals or at the time urine becomes sugar free. Get R B C, hemoglobin W B C, differential, and Wasserman.
- 9 Regular insulin units 50 in two locations intramuscularly stat. If blood pressure is low use intravenous route. Follow this with regular insulin units 20 intramuscularly every hour until urine is sugar free. At this point obtain blood for sugar and CO₂.
- 10 After four hours administer 20 gm of fluid carbohydrate every two hours. This may be administered by any indicated route except rectally. If blood sugar remains low when oral route alone is utilized, the intravenous route should be chosen, especially if urine still contains ketones.
- 11 Hypodermoclysis 1500 cc normal saline stat. Repeat after 12 hours if total fluid intake is below 3,000 cc. Keep solution warm.

- 12 Force fluids by mouth. If patient is vomiting or in coma, administer 120 cc (normal saline) rectally every two hours. If necessary administer 500 cc or more of normal saline intravenously every 8 hours to make up fluids to at least 5,000 cc first 24 hours.
- 13 If CO_2 is below 15%, sodium bicarbonate or sodium lactate may shorten the period of severe acidosis. This is most effective intravenously in 4% solution. The amount should not exceed 500 cc. Great care should be exercised not to permit the alkali outside of the vein because of the danger of a slough.
- 14 Record immediately on the Diabetic Acidosis Wall Chart the results of all tests and all administrations to the patient.

Carrying Orders

- 1 When urine is sugar free, inject 300 cc 10% glucose intravenously.
- 2 Omit insulin for two hours. Then change insulin order to read units 15 every two hours for 16 hours.
- 3 Continue fluid carbohydrate 20 gm every two hours for 16 hours. The preferable route will be indicated by the condition of the patient.
- 4 When patient is able to take nourishment, a bland diet containing protein 60 gm, fat 120 gm, carbohydrate 250 gm should be prescribed. This diet should be divided into four meals given four hours apart. The glucose equivalent of the foods not eaten or vomited must be made up with glucose within the hour after the meal.
- 5 Examine urine every four hours obtaining specimens before meals, at midnight, and at 4 a.m. Ten or more units of old insulin are administered if urine contains large amounts of sugar.

According to this plan, during the first 24 hours the patient should receive 200 gm of fluid carbohydrate. This can be given as orange juice, ginger ale, or glucose intravenously. If emesis occurs, replace the lost carbohydrate with glucose intravenously. For the first 24 hours after recovery, the diet may have to be liquid, changing to soft when tolerated, and soon to a bland diet and later to a usual diabetic diet.

One must be on guard against the development of hypoglycemia during the recovery period following acidosis. It is to be expected that the islands will resume a certain proportion of their pre-acidosis function and the return of this endogenous insulin secretion should be anticipated.

We have not yet used protamine zinc insulin as part of the treatment of diabetic acidosis. Quick action is desirable and old or crystalline insulin, of course, is preferable from that point of view. It has been proposed that a reservoir of protamine zinc insulin might be of value as a sustaining dose, but it is our opinion that it is better to leave a situation which is changing rapidly in a more flexible state, so that possible hypoglycemia can be combatted more effectively.

It is, however, very likely that when normal conditions for a given diabetic are re-established, that a change over to protamine zinc insulin is desirable. Our method of doing this has been established elsewhere (3) and will not be reviewed at this time. We would like to go on record, however, to the effect that, in our opinion, protamine zinc insulin is the insulin of choice in the routine treatment of uncomplicated diabetes.

There follows a sample of Diabetic Acidosis Wall Chart which we have used to record the progress of the patient in diabetic acidosis, and to make available for everyone connected with his care, the data which are the determining factors as to what to do next. We are aware of no single factor which has simplified treatment so much and which summarizes essential facts so completely and so promptly. One can tell at a glance, if orders have not been timely, and also, be certain that no one on the team has faltered. We have used this wall chart for ten years and have found it very useful.

Because urinalyses are most frequently used as a guide to carbohydrate needs and insulin and fluid requirements it is given first place on the chart. The data for sugar, diacetic acid and volume and the total volume are recorded hourly so one can know quickly if therapy is falling behind schedule. The urine volume is a good index as to whether or not the fluid and salt needs are being met adequately.

NAME _____		CASE NO. _____		DATE _____		DIABETIC ACIDOSIS WALL CHART	
TIME							
U R I N E	SUGAR						
	DIACETIC ACID						
	VOLUME CC						
	TOTAL VOLUME						
B L O O D	SUGAR						
	CO_2						
	CHLORIDES						
INSULIN (OLD)							
F L U I D	MOUTH						
	SKIN						
	VEIN						
	RECTUM						
	TOTAL						
CARBOHYDRATE (GMS)							
BLOOD PRESSURE							
TEMPERATURE							
PULSE							
RESPIRATIONS							
MEDICATIONS							
CLINICAL NOTES							

Chart 1

The record of the blood sugar CO_2 , and chlorides is kept in the next three spaces. From the data obtained from the examination of the urine and blood, insulin doses are increased or decreased according to the needs revealed.

Fluid intake by the four routes, mouth, skin, vein, rectum, are totaled so that one may be sure that adequate quantities have been administered to correct the marked dehydration occasioned by the polyuria and inorganic salt loss.

In the next space, carbohydrate intake, by grams is recorded as it is administered. The amounts are calculated from the quantities contained in the fluids

given and recorded above. The amount may need to be increased rather promptly, if the utilization as indexed by urine and blood analyses reveals it to be inadequate.

In view of the relatively large doses of insulin, it is probably unwise to permit the blood sugar to fall below 150 mgm per 100 cc or the urine to remain totally sugar free for any length of time. This is particularly important if the urine still contains ketones. Hypoglycemia is to be carefully avoided because of its shock producing effect. Patients, clinically, will change rapidly from being quite comfortable to being quite miserable in the presence of hypoglycemia.

The blood pressure readings are extremely important because a falling blood pressure indicates inadequate amounts of fluid and salt, and may even be severe enough to warrant stimulation with drugs or the use of the more effective and lasting therapeutic measure, transfusion. This latter will rarely be found necessary if sufficient water, salt and glucose are administered.

The temperature record indexes the need for the use of external heat or the need for discontinuing this. Patients should not be swathed in blankets and permitted to be drenched with sweat for by so doing one is permitting the loss of valuable salt and fluids and even, at times, causing an artificial or physical hyperthermia. This procedure may even lead to circulatory collapse and should be studiously avoided.

The pulse should be carefully watched for signs of cardiac weakness and the first indication of such a condition will be a rise in rate. An abrupt rise in rate should cause one to be suspicious of impending hypoglycemia and appropriate observations and therapy will prevent this condition from developing to a serious degree.

Respirations during ketosis are usually elevated. A fall in rate is a favorable indication of adequate treatment and is a fairly reliable index of changes in the severity of the acidosis. This, however, is not always true, for patients are seen in severe ketosis without respiratory rate changes. Such cases, however, are the exception rather than the rule. If the respiratory rate continues high when the acidosis is apparently controlled, other causes for this increase are to be sought for carefully.

Other medications than fluids, salt, glucose and insulin are recorded in the next space and usually have to do with the complication which precipitated the acidosis. It base is administered it should be recorded and taken into account to weigh the significance of the changed blood analyses. In this way one will not be deceived as to the true condition of the patient.

Clinical notes should be frequent and meaningful. Of particular importance are vomiting and diarrhea and sweating, changes in the mental status, and notes regarding bowel function and the ability of the patient to take and retain fluids. If food is vomited, a rough estimation of the quantities lost should be made available in order that this may be replaced by a parenteral route.

Chart 2 records the data obtained on one patient following the method of procedure which we have just outlined. It will be noted that urine volume was good from the start that the amount of sugar in the urine did not decrease below complete reduction but the amount of diacetic acid did decrease. The blood sugar estimations reveal a gradual drop, and the blood CO₂ a slow rise.

Hour	1	2	3	4	5	6	7	8	9	10	11	12
Urine Volume	150	250	450	150		150	300	150	250	200	250	250
Urine Sugar												
Blood Sugar			170			168				155		
Blood CO ₂		19.5				22.5				24.8		
B.P.			96/60	97/60	96/60	96/60	97/60	97/60	97/60	99/60	99/60	99/60
T	96.4		97.4			96	98.4	97.4	97	99.4	99	99
P	120		152	160	112	104	108	104	96	96	98	98
R	24		30	28	24	24	24	24	24	24	24	24
Respiratory	20	20	20	20	20	60	20	20	20	20	20	20
Total Glucose			20	20	30	20	25	20	20	20	20	20
F	450	150	200	150	600	450	200	500	200	300	300	300
U						300						
V												
D												
Total			450	600	800	1250	1850	2500	2500	3000	3200	5000
Order		Enema										
Notes		Drainage of ear	Enema	Enema	Enema	Enema	Enema	Enema	Enema	Enema	Enema	Enema

Acidosis (Diabetic) Mill Chart
Chart 2

When the blood pressure was noted to be falling caffeine was administered.

The temperature was 96.4 on admission but by the tenth hour was above normal. The pulse rate after the fourth hour showed a gradual decline and the respiration rate approached normal.

The insulin schedule of 20 units per hour was deemed inadequate by the sixth hour and a large dose of 60 units was administered at this time. Carbohydrate administration was started beginning with the fourth hour, and continued at the approximate rate of 20 gms per hour. Fluids were tolerated by mouth after the third hour but were not adequate. Hypodermoclysis was started and permitted to run continuously for the next nine hours. In the 6th hour 300 cc of 10% glucose were given intravenously which effectively bolstered the falling blood pressure. Total fluids in the first twelve hours was 5000 cc.

The patient improved satisfactorily from the start. Vomiting occurred only once and recovery was uneventful.

Chart 3 shows graphically the eight day course of W. B., a colored female, age 20 years weighing 87 lbs. Her estimated normal weight was 124 lbs.

Three months before admission this patient suddenly developed severe polydipsia, polyuria and polyphagia. Two months before admission, she complained of severe headaches which were diagnosed as migraine. She had several vomiting spells, became unconscious and remained so for four days when she was admitted to a Detroit hospital and treated successfully for diabetic acidosis.

Shortly after her recovery from this episode, she developed an infected ear which was lanced and had drained pus since that time. She continued to lose weight from February to May dropping from 110 lbs to 87 lbs observed on admission to the hos-

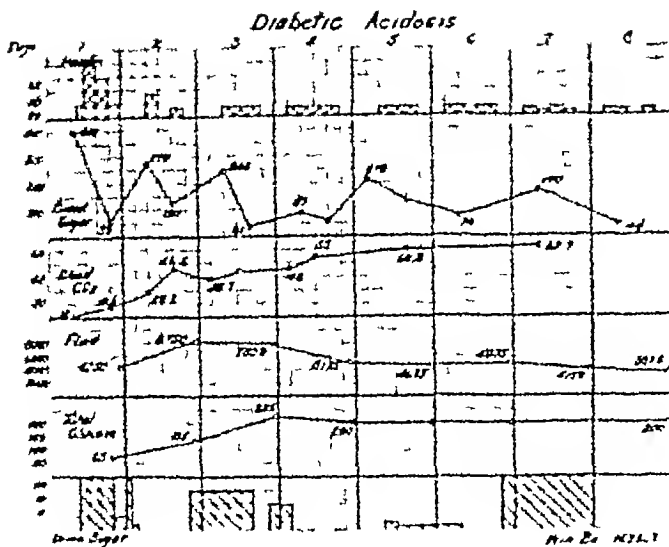


Chart 3

pital. Her chief complaint on admission was shortness of breath. Diabetic acidosis was diagnosed and treated with the result recorded on the chart.

It is noted on admission that the blood sugar was 400 mgm per 100 cc and the blood CO₂ 12 vol per cent. In 12 hours the CO₂ had risen to 18.6%. The blood sugar had dropped to hypoglycemic levels. She had received during this time only 65 gms of glucose and there had been administered 160 units of insulin. On the second day her course was less stormy; only 45 units of insulin were administered, and the urine remained sugar free most of the day and the blood sugar relatively well controlled. On the third day the patient slipped into acidosis again and it is to be noted that 45 units of insulin created hypoglycemia. After this day her course was uneventful.

It is evident that this patient received too much insulin and too little glucose during her first two days of treatment.

Chart 5 records the seven day hospital admission of J. M., a male, age 53, weighing 174 lbs with a estimated normal weight of 166 lbs.

He had had diabetes for eight years and was accustomed to use 20 units of old insulin daily. He

made no pretense of dieting. Five days before admission he developed nausea and vomiting which persisted until he entered the hospital. He had reduced his insulin dosage to 10 units. He had noted a marked thirst during these 5 days. He became semi-comatose on the second day before admission and had been in deep coma for 24 hours when first seen. The diagnosis of diabetic coma was easily made and treatment instituted.

His blood sugar was 545 mgm per 100 cc and the blood CO₂ 19.5 vol per cent. During the first 12 hours he received 8100 cc of fluid and 185 gm of glucose and 190 units of insulin. On the second day the blood sugar was well controlled and the CO₂ rose to 49.5 volumes per cent. He received this day 6000 cc of fluid and 350 gm of carbohydrate and 280 units of insulin.

It is interesting to note that on the 7th day the blood sugar was controlled at 125 mgm per 100 cc. He consumed 140 gm of carbohydrate and required but 55 units of insulin.

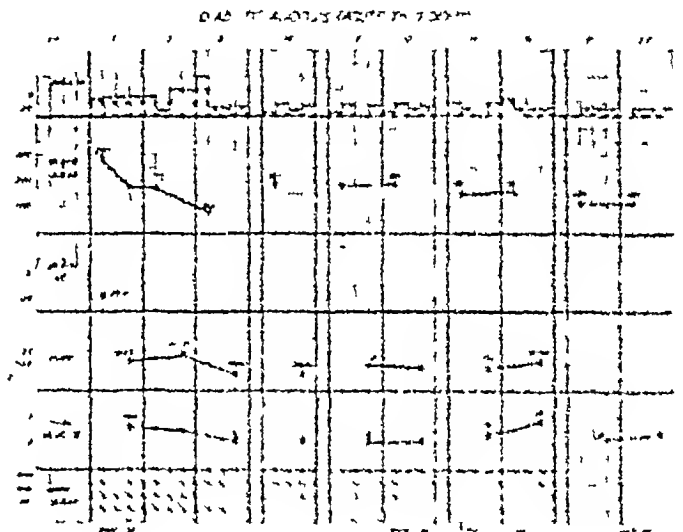


Chart 5

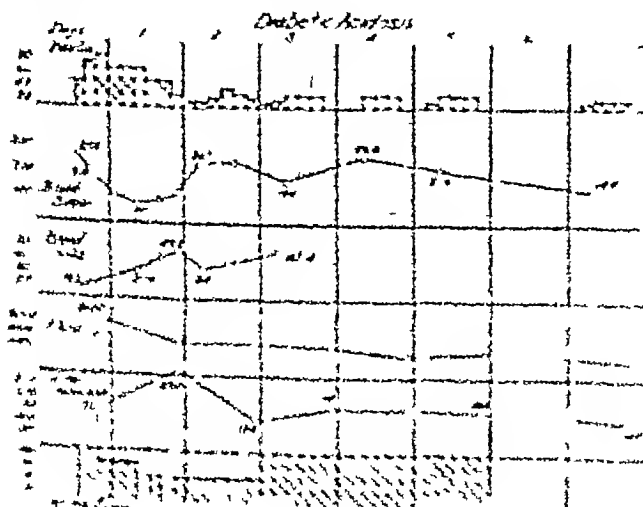


Chart 4

His insulin dose, for control, changed from 15 units daily to 100. A B M R was taken on the day before acidosis developed and is recorded as plus 34%. He was brought out of acidosis with some difficulty and stabilized on a liberal diet and adequate insulin dosage. Thyroidectomy was performed 16 days after the development of an acute thyroiditis.

His course following operation was in no way stormy. The sugar disappeared from his urine and the blood sugar remained normal after the fourth post-operative day. This is the only case of acute thyroiditis and diabetes that we have ever observed.

DISCUSSION

We now turn to the discussion of 83 instances of diabetic acidosis. These patients are divided into two groups. The first group of 50 patients, called Group I, were treated before 1931. The second group, called Group II, were treated in 1937, 1938, 1939. The latter group contains 32 cases. For the most part these patients if under treatment at all before their acidosis were receiving protamine zinc insulin. We wish to determine for one thing whether or not the introduction of protamine zinc insulin had modified in any way the development of acidosis. The series of tables which follow compares the salient features of the two groups.

Table 1 The average age of the two groups remains unchanged the oldest being 80 years in Group I and 72 in Group II. Children were excluded from Group II, whereas there were three cases included in Group I. Weighing the average, with this fact in view, one might say that before 1931, the age of the occurrence of the acidosis was slightly higher but not significantly so.

Table 2 Age Distribution. This tabulation reveals a larger percentage of acidosis in the elderly, but again the inclusion of three children in the first group modified this picture appreciably. If the children were eliminated, the percentage of patients under 20 years would be only 10%. The reason for this shift is not apparent unless one wishes to take into consideration the fact that diabetics are living to an older age.

Table 3 The sex ratios of the two groups remain unchanged with females still predominating. This is to be expected when one considers the possibility of glandular upsets in the female. It is now quite generally conceded that diabetes mellitus is not due solely to pancreatic deficiency, but that the picture is colored by abnormalities of pituitary, thyroid and adrenal secretion. The function of these latter three glands is disturbed much more often in the female than in the male. It is interesting to mention at this point that the reported increase in the incidence of diabetes itself is confined almost wholly to females who have reached the usual age of menopause.

Table 4 Weight Distribution. The figures showing the incidence of acidosis in persons over or under weight are quite significant. They bear out our impression that the diabetic most difficult to control is the thin diabetic. The general trend in the two groups

is essentially similar. Approximately 63% of the patients studied in the combined series were underweight. Only 9% of Group I were overweight whereas 17% of Group II were overweight. This change of incidence may be a reflection of the tendency now to maintain diabetics in a better state of nutrition.

It is quite evident from these figures that one should warn the underweight diabetic more emphatically of his increased susceptibility to acidosis and lay particular emphasis on what to do about it if it should occur. He should be warned of the most common initial symptoms of acidosis—namely nausea, vomiting, headache or a return of the cardinal symptoms of the disease.

Table 5 The most common causes of acidosis are tabulated. The distribution of causes in both groups is similar except in one or two instances. Infection still heads the list and carelessness about diets still occupies second places.

On breaking down the percentage of insulin errors in Group II we discover that there were three instances of acidosis which were due to spoiled insulin. This fact should lead one to emphasize to the patient that old insulin if cloudy or discolored has no potency and that the dates on the bottles of protamine zinc insulin are to be scrutinized. If the expiration date has been passed the insulin should be refused.

Further, protamine insulin is the cause of more allergic phenomenon than old insulin. The only fatal one in Group II, which could be attributed directly to acidosis, was in a patient who became violently sensitive to insulin of all types. We have observed two such cases but the other one was successfully desensitized and recovered.

One patient developed acidosis while being changed over from old insulin to protamine zinc insulin. This occurred during our early experiences with protamine zinc insulin and need never happen again with the knowledge which we now possess.

Patients omit insulin under the influence of misleading advertisements and should be warned that up to the present no "by mouth" preparation is potent.

Table 6 Patients still continue to have symptoms of acidosis too long before seeking help. Education is the answer to this problem. The usual period intervening between onset of symptoms and treatment is from two to three days. This happens even in diabetics whom one considers to be very well instructed. Possibly the acidosis itself causes a sluggish mental response in the patient to his emergency. The correction for this would seem to be to make certain that others in the family beside the diabetic himself were also educated to recognize the danger signals of acidosis.

Table 7 The highest blood sugar value recorded in this series is 668 mgm per 100 cc, the lowest 77 mgm. The average blood sugar was 385 mgm per 100 cc. The percentage of blood sugar values which fall outside of the range of 200 to 600 mgm is negligible. The only warning to be sounded is that many

patients, since the discovery of insulin, have been given this drug before they enter the hospital and the finding of a low blood sugar should not deter one from making a correct diagnosis. A larger percentage of lower blood sugars occurred in Group II, which fact might be attributable to such a cause.

Table 8 The figures for the blood CO₂ in the two groups are almost identical. Apparently patients in 1937, 1938, 1939 permit the same degree of acidosis to develop before seeking aid as was the case during the earlier years.

Table 9 The distribution of light and severe instances of acidosis as indexed by estimations of the blood carbon dioxide combining power is practically identical in the two groups.

Table 10 As will be noted, by examining the tabulation of the Blood Non-Protein-Nitrogen this metabolite is apt to have accumulated over the normal limit even in the absence of renal disease. This abnormality is usually quickly rectified when the blood chlorides are restored to normal. No special therapy for its correction is indicated. One can assume that with the low blood pressure, so frequently observed that renal function is disturbed, and it is also well known that non-protein nitrogen and blood chlorides have a reciprocal relationship. When the hypochloremia is corrected the elevated non-protein nitrogen disappears.

Table 11 The data on blood chlorides reveals that they may be quite depressed in some instances and on the average are definitely below the optimum. This finding, of course, is anticipated from the very nature of the metabolic disturbances and gives adequate logic to the liberal use of chlorides in therapy.

Table 12 The average white blood count of Group II was 12,768. This figure is tabulated from the examinations on patients without evident infection. That the white count is elevated in uncomplicated acidosis has been emphasized by many authors and is mentioned again here to warn against unnecessary surgery and alarm when it is observed. Because abdominal symptoms, simulating acute infection, are among those most commonly observed in diabetic acidosis, such a warning is not untimely.

Table 13 The distribution of blood pressure readings in the two groups is unchanged. It is to be noted that some very low readings are recorded but that the average approaches normal. Blood pressures below 100 systolic have grave prognostic import and demand immediate treatment.

Table 14 Temperature. It is to be noted that even though some of these patients were suffering severe infections, temperatures were not tremendously high. Of much more significance is the record of sub-normal temperature. The patient in acidosis is in shock and the temperatures are not parallel with the degree of abnormal physiology involved. One explanation for the low temperature is to be found in the disturbed burning of foods. In order to restore the temperature to normal not only must the loss of heat from the body be interrupted, but many times, external heat needs to be supplied.

Table 16 Respirations are usually elevated during an existing acidosis. Extremely high rates are observed in Group II up to 48 per minute. It is of interest to note, however, that in some instances the rate is below normal and this observation alone cannot exclude the existence of an acidosis. The rate of 10 in Group I, was observed in a patient with cerebral hemorrhage. The average rate was 26 in both groups.

Table 16 The average pre-acidosis daily insulin dose of both groups was in the low thirties. Such patients are usually classed as moderately severe diabetics and it would seem that this group is more apt to develop acidosis. Possibly this is because they take their diabetes less seriously and commit more diabetic errors.

Table 17 Pre-acidosis diet. It is of no little interest to compare the pre-acidosis diets of these two groups. It can be noted at a glance that the carbohydrate content of Group I is much lower than that of Group II. During the past decade the carbohydrate content of the diabetics diet, in most clinics, has increased. In comparing these two groups the amount has more than doubled during the period of observation.

That this change has been gradual is illustrated very well in Chart 6. This study was made on a group of thyro-diabetics observed from 1925 to 1936 and illustrates the gradual increase in the carbohydrate

AVERAGE DIETS BY YEARS			
Year	Diet		
	Protein	Fat	CHO
1925	51	140	63
1926	58	161	76
1927	60	200	80
1928	60	185	97
1929	62	160	100
1930	57	166	98
1931	61	153	123
1934	61	103	153
1935	67	201	212
1936	70	220	250

Chart 6

allowances of patients having both diabetes and hyperthyroidism. Since 1931 the increase has been quite consistent and rather rapid. Whether this increase in carbohydrate has caused the occurrence of acidosis to be less common is not answered by this study, but our impression is, that this is so.

Table 18 The average duration of acidosis in Group II is 37 hours. This figure is not accurate because of the infrequency of CO₂ estimations and the actual duration of the acidosis is probably less than this. If

this is so, a change should be made in the vigor with which we treat this condition

Table 19 Mortality In the first group of 50 patients, 9 died giving a gross mortality rate of 18%. The acidosis was the chief factor as the cause of death in one case (2%). The remaining cases died of the causes as tabulated

Table 20 In Group II, consisting of 32 cases, 5 died (15.1%). Acidosis was the chief factor in one case (3.1%). The other causes of death are as tabulated

SUMMARY

Studies by hundreds have been made to determine the most efficient method of using insulin, fluids, salt, and glucose to combat diabetic acidosis. Team work is demanded for success. Before the days of insulin few patients recovered whose carbon dioxide combining power was less than 20%. Now there are many records of recovery with the carbon dioxide combining power of the blood below 10%.

The treatment of diabetic acidosis requires hospitalization in order to reestablish normal quantitative values for the chemically altered body fluids. Normal body temperature, blood pressure, and renal function should be reestablished as soon as possible.

Carbohydrate should be administered as soon as the blood sugar estimations reveal a decided decline. Hypoglycemia should be avoided.

Dehydration should be combatted vigorously with salt solution. Patients utilize, with benefit, 5000 to 8000 cc of fluid in the first 24 hours.

If the circulation is sluggish intravenous and intramuscular insulin is advisable. The intensive treatment schedule should not be discarded too soon, or a relapse may occur. When a regular diet is resumed a high carbohydrate (200 gm.) allowance should be provided.

A detailed tabulation of initial order is outlined, followed by carrying orders to be adopted when the acidosis is corrected.

Protamine Zinc Insulin has no part in the treatment of diabetic acidosis, but is the insulin of choice for the routine care of most patients.

A sample of the "Diabetic Acidosis Wall Chart" used, to record the progress of the patient in diabetic acidosis is shown. It makes available for everyone connected with the care of the patient all the therapeutic procedures and the patient's response to them.

Data of four actual clinical cases is given in detail.

A statistical study of 83 instances of diabetic acidosis is presented. These cases are divided into two groups: Group I consisting of patients treated before 1931, Group II treated in 1937-1938 and 1939.

The average age of the two groups remained unchanged as did the sex ratio. Underweight diabetics were more frequently affected. Infection heads the list as the most common cause of acidosis and dietary errors occupy second place. Insulin errors seem to be becoming a more frequent cause. Patients still omit insulin under the influence of misleading advertisements.

Symptoms of acidosis are usually present from 2 to 3 days before medical advice is sought. Probably the

acidosis itself causes a sluggish mental response in the patient to his emergency. Other members of the family should be educated to recognize the danger signals of impending acidosis.

The average blood sugar on admission was 385 mgm. per 100 cc and the average carbon dioxide combining power of the blood was 24 volumes per cent.

The non-protein nitrogen is usually elevated but is quickly rectified. The blood chlorides are below normal.

The white count averaged 12,768 and deserves special mention because abdominal symptoms simulating acute infection are among those most commonly observed in diabetic acidosis.

The blood pressure average approaches normal but is low in many individual instances and calls for immediate treatment. Respirations average 26 per minute but in individual instances may be normal or increased to as high as 48 per minute.

The average pre-acidosis insulin dose was 34½ units daily. The pre-acidosis diet has a higher carbohydrate content in those patients in Group II.

The average duration of the acidosis after treatment was started was 37 hours. This figure is not accurate because the frequency of CO₂ determinations was inadequate to settle this point.

The mortality rate if corrected to include only those cases where acidosis was the chief factor, was 2% in Group I and 3.1% in Group II. A tabulation of the other causes of death is presented.

CONCLUSIONS

The general picture of diabetic acidosis remains unchanged during the past decade. An hourly "Diabetic Acidosis Wall Chart" we believe aids in coordinating the efforts of those responsible for the treatment of the patient. It seems doubtful to expect a greatly improved result until some new principle of treatment is forthcoming.

TABLE 1

Age		Group 1	Group 2
Oldest	-	80 yrs	72 yrs
Youngest	-	4 yrs	20 yrs
Average	-	44 yrs	43 yrs

TABLE 2

Distribution		Group 1	Group 2
1 - 20 yrs.	-	16%	3%
21 - 40 yrs.	-	32%	53%
41 - 60 yrs.	-	44%	22%
61 - 80 yrs.	-	8%	22%

TABLE 3

Sex		Group 1	Group 2
Males	-	22 - 44%	13 - 40.6%
Females	-	28 - 56%	19 - 59.4%

TABLE 4

Height Distribution		Group 1	Group 2
Normal limits	-	26.6%	20.2%
10 - 19% overweight	-	4.4%	7.0%
20% or more	-	4.4%	10.4%
10 - 19% underweight	-	33.3%	45.0%
20% or more	-	31.1%	17.4%

TABLE 5
Causes of Acidosis

	Group 1	Group 2
Infection	46%	35.7%
Faulty diet	20%	21.4%
Insulin error	18%	23.8%
G I upset	4%	9.5%
Other causes	12%	9.6%

Some cases had multiple causation

TABLE 6
Duration of Acidosis Symptoms

	Group 1	Group 2
High	7 days	14 days
Low	1 day	1 day
Average	2.4 days	3 days

TABLE 7
Distribution of Blood Sugar Values

	Group 1	Group 2
101-200 mgms	6%	16%
201-300 mgms	28%	13%
301-400 mgms	38%	27%
401-500 mgms	24%	19%
501-600 mgms	4%	16%
601-668 mgms	0%	9%

TABLE 8
Blood Carbon Dioxide

	Group 1	Group 2
High	56.0 vol %	54.1 vol %
Low	10.1 vol %	12.0 vol %
Average	25.9 vol %	24 vol %

TABLE 9
Blood Carbon Dioxide Distribution

	Group 1	Group 2
10-20	vol % 34.7%	41.9%
21-30	vol % 32.6%	32.3%
31-40	vol % 28.2%	22.6%
41-50	vol % 2.1%	0.0%
51-56	vol % 2.1%	3.2%

TABLE 10
Blood Non-Protein-Nitrogen

	Group 1	Group 2
High	60.8 mgm /100cc	143 mgm
Low	20.0 mgm /100cc	24 mgm
Average	37.0 mgm /100cc	58.8 mgm

TABLE 11
Blood Chlorides

	Group 2
High	574 mgm /100cc
Low	350 mgm /100cc
Average	432 mgm /100cc

TABLE 12
White Blood Count

	Group 2
High	21,800
Low	4,400
Average	12,768

TABLE 13
Blood Pressure

	Group 1	Group 2
Below 110	33.3%	34.7%
High (systolic)	185	218
Low	80	78
Average	121	121
High (diastolic)	140	100
Low	42	54
Average	74	73

TABLE 14
Temperature

	Group 1	Group 2
High	100.0	101.2
Low	96.0	95.0
Average	97.2	98.2

Infection excluded

TABLE 15
Respiration

	Group 1	Group 2
High	40	48
Low	10	16
Average	26	26

TABLE 16
Insulin

	Group 1	Group 2
Average units daily	32	34.5

TABLE 17
Pre-Acidosis Diet

	Group 1	Group 2
PFC	PFC	PFC
High	65 205 150	79 250 250
Low	40 90 45	55 70 60
Average	56 147 84	69 164 194.2

TABLE 18
Duration of Acidosis

	Group 2
High	84 hours
Low	7 hours
Average	37 hours

Recovery CO₂ above 40 vol %

TABLE 19
Mortality

	Group 1
Total 9 cases	18%
Acidosis chief factor	1 case 2%

OTHER CAUSES OF DEATH

Cerebral hemorrhage	1 "
Myocardial insuff	1 "
Gangrene, amputation	2 "
Pneumonia	3 "
Pyelonephritis	1 "

TABLE 20
Mortality

	Group 2
Total 5 cases	15.7%
Acidosis chief factor	1 case 31%

(This case allergic to insulin)

OTHER CAUSES OF DEATH

Pneumonia	1 "
Acute Pul Tbc	1 "
Coronary Occlu	1 "
Gangrene amputation	1 "

(Hgb 5 gms)

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Report of a Case of Diverticulum of the Stomach (Cardia)

By

B. RESNICK, 1st Lt. M.C.

HOCA RATON FIELD, FLA.

THIS case is reported because of its rarity and because clinically the symptomatology may simulate any form of a gastric disorder, particularly gastric ulcer. As a good gastro-intestinal study is essential, one should never omit examining the patient in the Trendelenburg position as the diagnosis may be otherwise missed.

CASE REPORT

Private C, a 23 year old, white male was admitted on February 2, 1943 to the Station Hospital, complaining of epigastric pain, vomiting and eructations of 24 hours duration.

In the past he had had similar attacks without vomiting periodically since October, 1942. In February of 1941 he suffered from pain after meals and after radiography was told he had a peptic ulcer. Treatment at that time consisted of a Sippy regimen. Under this therapy his symptoms abated and he remained well, entering the Army on July 22, 1942. Since October he has had recurrences of his abdominal discomfort. This consisted of pyrosis with epigastric pain non-radiating, often accompanied by nausea but no vomiting. The pain recurred regularly one hour after meals and was relieved by food and alkalies. There was no history of dysphagia, anorexia, loss of weight, icterus, acholic stools, haematemesis or melena.

His habits were not contributory except that he smokes and drinks moderately. His family history was significant in that his father, sister and brother have undergone therapy for peptic ulcer.

Physical examination revealed a healthy appearing adult male, in no apparent distress. Temperature, blood pressure and pulse rate were within normal limits. The organs of special sense showed no abnormality. The thyroid gland was slightly enlarged bilaterally, no nodules were palpable and no bruit was evident. The lungs were clear to percussion and auscultation. The heart was not enlarged, the mechanism was normal and the sounds were of normal quality and intensity. Abdominal examination revealed some epigastric tenderness on deep palpation. There was no rigidity or spasm, no masses were present. The liver, spleen and kidneys were not palpable. Digital rectal examination was negative. Examination of the locomotor organs and nervous system was negative.

Laboratory findings were as follows:

Blood — Hgb — 90%, RBC — 5,160,000
WBC — 7,150 normal differential
Urine Analysis — No abnormality

Scrology Kahn, doubtful (3 times) Wassermann—Negative.

Gastric Analysis Free HCl — 20°; Combined HCl — 35° Total — 55°

A working diagnosis of gastric ulcer was made. The radiographs obtained are illustrated below.



Fig. 1 Shows an outline of the stomach in lateral projection. An un-filled diverticular sac with a narrow pedicle is present on the posterior aspect of the cardiac end of the stomach. The sac is smooth rounded, and measures 1 1/2 cm. and the mucosa is stained with Barium.

As the patient's symptoms abated under bed rest and regulated regimen he was discharged after two weeks of comfort. No operative interference was considered as long as the patient improved under medical supervision.

COMMENT

It is interesting to correlate the clinical symptoms with the radiographic findings. The patient has had long periods of freedom from symptoms punctuated by periodic bouts of discomfort from a mechanical point



Fig 2 Shows the stomach in lateral projection. The patient lies in the Trendelenburg position. The pouch is now completely filled with the media.

of view it is difficult to see how pain would be caused by pressure alone. Many instances of diverticula of comparatively large size are known to be asymptomatic. The patient's attacks of pain, nausea and vomiting are probably brought on by any agent causing gastritis, such as dietary indiscretion. However, due to the presence of the sac, a local state of stagnation is present. The walls of the sac are swollen and edematous and because of the narrow pedicle, the sac has difficulty in emptying and a resulting diverticulitis with secondary inflammatory changes in the walls is present, and the symptomatology ensues. When the sac can empty freely again and the inflammation subsides the discomfort ceases.



Fig 3 Shows a barium residue in the sac. This Postero-anterior projection was taken six hours after the ingestion of the media.

The differential diagnosis must be made from that of perforating gastric ulcer with an accessory pocket. While the history is typical of the ulcer syndrome, the site of the lesion close to the oesophageal orifice is not the usual one. Anomalies of development are more apt to occur at this site and radiographically the smooth contour of the sac and lack of infiltration of the walls of the stomach are in keeping with the diagnosis of diverticulum.

SUMMARY

A case of diverticulum of the cardiac portion of the stomach is presented with radiographic studies. An attempt is made to explain the recurrent nature of the symptoms on an obstructive and inflammatory basis.

The Absorption of Iron from Ferrous Sulfate with Observations on Hemoglobin Changes and the Influence of Certain Intestinal Protozoa*

By

ALICE G. MARSH, M.S.
RUTH M. LEVERTON, Ph.D.
THELMA J. McMILLAN, M.S.

and

GEORGE R. LINDERWOOD, M.D.
LINCOLN, NEBRASKA

RECENT research has altered our concept of the body's management of iron whether this dietary essential is administered orally or by injection. It was formerly believed that catabolized iron, and iron in excess of that used for hemoglobin formation and maintenance of normal body stores, was excreted by way of the intestine. It has now been established that the body does not have the ability to excrete iron but that the iron in the feces is that which has passed through the intestine unabsorbed (1, 2). This has led to the suggestion that the body controls the metabolism of iron by regulation of the amount absorbed rather than the amount excreted (1).

The present study was undertaken in an effort to answer several questions which arise when iron absorption and excretion are viewed from the standpoint of this newer concept of the body's inability to excrete iron. The questions are these: (a) When an iron concentrate such as ferrous sulfate is given orally for several successive weeks will the body regulate its absorption so that as the body's store of iron increases there will be a decrease in the amount that is absorbed as the period of therapy proceeds? (b) Since the quantity of iron that is absorbed during such periods greatly exceeds any calculated need or reasonable use by the body will this excess gradually be released after the concentrate is discontinued and the pressure of a high concentration of iron in the intestinal contents is removed? and (c) do certain protozoa frequently present in the intestinal tract interfere with iron absorption and hemoglobin formation?

PROCEDURE

Intestine studies of the absorption and excretion of iron were made on 46 healthy college women. Thirty-three of these studies dealt mainly with the absorption of iron from an iron supplement which was given daily for five or six weeks while the other 17 studies (13 subjects) were concerned primarily with the excretion of iron after such a supplement had been discontinued. In the excretion tests the supplement was given for only one week. All the subjects were on their customary self-chosen diets which previous study had shown furnished an average of 10 mg. of iron daily. The daily supplement was 126 mg. of iron furnished by two three grain

ferrous sulfate tablets taken with the morning meal. Stools were collected for all subjects during the time the ferrous sulfate was given, and for the 13 subjects who had the supplement for only one week, for the seven days preceding and for the 30 days following the supplement.

The gross effect of certain pathogenic and non-pathogenic micro-organisms of the intestinal tract upon the absorption of iron was determined in the group of 33 subjects. Microscopic examination of the fresh liquid stools that were passed after a purge of Epsom salts showed that 12 subjects had no protozoa. 13 subjects were infected with *Endamoeba histolytica*, and eight others had various flagellates as well as non-pathogenic amoebae of which *Endamoeba coli*, *Entodina nana*, and *Iodamoeba buetschlii* were most common. Ferrous sulfate was given for three weeks, and then the subjects who had been found to harbor these protozoa were treated with carbarsone to rid them of these micro-organisms. At least to the extent that another microscopic test was negative, they were then given ferrous sulfate again for two or three weeks.

Collection of stools and their preparation for analysis were made as previously described by Leverton and Marsh (3). Iron was determined by the thiocyanate method as developed by Sturgart (4) and all colorimetric readings were made in a Sanford-Sheard photometer.

Routine hemoglobin examinations were made on all subjects by the method described by Todd and Sanford (5) and the fully developed oxyhemoglobin was read in the photometer.

RESULTS

Figures for the average daily absorption of iron by the subjects during the time when supplementary iron was given are shown in Table I. They are very similar regardless of whether the subjects received additional iron for one week or for six weeks or for any length of time between one and six weeks. The average daily absorption for the 33 subjects who were given 126 mg. of iron daily for a period of five or six weeks ranged from 64.79 mg. to 102.81 mg. with an average of 76.79 mg. This meant that from 47.6 per cent to 75.6 per cent of the total iron ingested each day (126 mg. from ferrous sulfate plus 10 mg. from the diet) was absorbed or an average of 56.5 per cent. For the 13 subjects who were given the supplement for only one

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week the average daily absorption of iron ranged from 46.71 mg to 116.17 mg with an average of 77.39 mg. The percentage of absorption for this shorter period ranged from 34.3 per cent to 85.4 per cent with an average of 57.4 per cent.

TABLE 1

The average daily absorption of iron during six weeks of high intake for 33 subjects classified according to the protozoal groups and for 13 subjects during one week of high intake.

		12 subjects with no protozoa	13 subjects with <i>E.</i> histolytica	8 subjects with non pathogenic protozoa	Average for 33 subjects	13 subjects not examined for protozoa
First week	mg	84.25	73.67	89.44	81.34	77.39 ¹
	%	61.9	54.2	65.8	59.8	57.4
Second week	mg	76.31	77.69	67.45	74.95	
	%	56.1	57.1	49.6	55.1	
Third week	mg	80.32	76.03	68.60 ²	76.01	
	%	59.1	55.9	50.4	55.9	
Protozoacide given						
Fourth week	mg	76.75	65.40	76.67	78.9 ²	
	%	56.5	60.6	56.4	58.1	
Fifth week	mg	78.45 ¹	80.71	71.26	75.05	
	%	57.7	59.3	52.4	55.2	
Sixth week	mg	74.41	76.3 ²	64.32 ³	73.26	
	%	54.7	56.1	47.3	53.9	
Average for entire period of supplement	mg	78.42	76.81	74.01	76.79	
	%	55.5	56.5	54.4	56.5	
Range of values for individual subjects—						
lowest	mg	64.70	66.23	67.19	64.79	46.71
highest	mg	74.71	102.81	84.20	102.81	116.17
lowest	%	47.6	48.7	49.4	47.6	34.3
highest	%	69.6	75.6	61.9	75.6	85.4

11 subjects

2, 7 subjects

3, 4 subjects

4. The ferrous sulfate supplement was forgotten one day by one subject.

Considering the individual variation in intestinal motility and that carnine was given to mark the stools at three-week intervals rather than at weekly ones, no significance can be attached to the small differences between the amounts of iron that were absorbed by the control subjects and by the subjects with certain protozoa, or between the average daily absorption for different weeks during the study.

The same is true of the subjects harboring the different protozoa and is shown by the figures in Table 2. Neither the presence of certain pathogenic and non-pathogenic protozoa, nor their absence after a protozoacide noticeably affected the absorption of iron by these subjects.

The increases that were taking place in the body stores of iron of all the subjects did not lead to significant changes in the hemoglobin content of the blood. The average hemoglobin value for the 33 subjects was 12.9 gm per 100 ml of blood at the beginning of the study and 13.0 gm after five or six weeks of iron supplementation. At the beginning of the study the average hemoglobin value for the 13 subjects was 13.5 gm, after one week of supplement 13.2 gm, and at the end of thirty days following the supplement, 13.1 gm.

The total amount of iron that was absorbed by the subjects who received the supplement for five or six weeks was sufficient to practically double the iron con-

tent of their bodies. The amounts that were absorbed ranged from 2,721 mg to 4,318 mg and averaged 3,225 mg. The total amounts of iron that were retained by the subjects who received the supplement for only one week averaged 542 mg.

TABLE 2

The absorption of iron and the hemoglobin values for subjects before and after a protozoacide and for their controls.

Subjects	Average daily absorption of iron during three weeks of iron supplement				Hemoglobin value, gm per 100 ml blood	
	Immediately before protozoacide		Immediately after protozoacide		Before protozoacide	After protozoacide
	mg	Per cent	mg	Per cent		
13 subjects with <i>E. histolytica</i>	75.80	55.7	79.83	58.7	13.0	13.0
8 subjects with non pathogenic protozoa	75.16	55.3	70.75	52.02	12.7	13.1
	First 3 weeks		Second 3 weeks		First 3 weeks	Second 3 weeks
12 control subjects with none of these	80.29	59.0	76.55	56.3	13.0	13.0

The data for the average daily fecal excretion of iron by the 13 subjects, whose stools were collected for 30 days after the supplement of iron was discontinued, are given in Table 3. The average daily excretion by the different individuals during the foreperiod or week preceding the period of high intake, ranged from 2.44 mg to 13.82 mg of iron with an average of 6.67 mg for all subjects. The ingestion of 126 mg of iron daily for one week increased the average daily excretion to 47.55 mg of iron. As soon as the supplement was discontinued there was a rapid diminution in the amount of iron that was excreted. During the first three days the average daily excretion for all subjects dropped to 31.27 mg, then the next three days it dropped further to 9.77 mg, and during the seventh to ninth days to 7.35 mg of iron per day. By the ninth day every subject was excreting approximately the same amount of iron as she had during the week before the supplement was given and she continued at this level with little variation for the ensuing three weeks or until the end of the study. The average total daily excretion for all the subjects for the last three weeks of the follow-up period was 6.17 mg of iron, in comparison to the average of 6.67 mg during the foreperiod at the beginning of the study. After the first six days of the follow-up period the range of excretion was very similar for each succeeding group of days. At no time during the follow-up period did the excretion of iron for any individual increase significantly or remain consistently at

TABLE 3

The average daily fecal excretion of iron of thirteen subjects for forty-four days.

	Length of period, days	Range		Average
		lowest mg	highest mg	
Foreperiod	7	2.44	13.82	6.67
Period of high intake (6 grains ferrous sulfate)	7	11.02	73.32	47.55
Follow-up period	30			
1st to 3rd day	3	4.99	70.88	31.27
4th to 6th day	3	4.07	24.53	9.77
7th to 9th day	3	2.02	19.43	7.35
10th to 16th day	7	2.84	10.74	6.56
17 to 23rd day	7	2.50	8.67	5.93
24th to 30th day	7	1.92	14.74	6.01

4 Despite the retention of the large amounts of iron there were no significant changes in the hemoglobin values

5 Twenty-one subjects infected with *E. histolytica*, or with other non-pathogenic amoebae and various flagellates, absorbed the same amount of iron before and after the administration of a protozoocide

6 These twenty-one subjects also absorbed the same amount of iron as the control subjects who were not infected with the micro-organisms

7 The average amount of iron absorbed, 76.79 mg per day, by the subjects who received the supplement for five or six weeks was as great as that reported in the literature for subjects who received eight times this amount of iron or the usual medicinal dose

8 During the thirty days that followed a week of iron supplementation the body did not release or excrete the iron that had been absorbed from the supplement

9 There was no indication that the body has an

ability to control the iron content of the body by excretion or absorption

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A Planned Dietary in the Treatment of Addison's Disease With Desoxycorticosterone Acetate*

B₃

THOMAS HODGKIN MCGAVACK, M.D., F.A.C.P.

and

LOUISE BABCOCK

NEW YORK, N. Y.

DESPITE some decrease in the cost of watery extracts of the whole adrenal cortex and the isolation and synthesis of many compounds simulating in effect one or more of the functions of that structure, desoxycorticosterone acetate remains the most readily available commercially of the 17-keto-steroids and the most powerful in its positive influence upon sodium and chloride metabolism.

Its use has spread far beyond the field of adrenocortical insufficiency, often with underemphasis upon the dangers deriving from its capacity for retaining sodium within the body and stabilizing the distribution and excretion of potassium. The fundamental synergistic relationship between desoxycorticosterone acetate and sodium in body metabolism has been so frequently demonstrated as to need no further elaboration here.

It has been shown in a clinical way (1) (2) (3) (4) that the effect of the drug is inversely proportional to the amount of sodium available for its action, according to the formula $D = \frac{k}{Na}$, where D represents the

daily intake of desoxycorticosterone acetate in milligrams, Na the daily ingestion of sodium in grams and k, a constant.

The value for k will necessarily vary as the degree of adrenal insufficiency present, but once established in a single individual, appears to remain strikingly constant. In the stabilization of seven patients with Addison's disease, the values for k have ranged from 37.5 to 45, with more than half of the determinations at the upper figure (4). Variations in the Na figure of this equation are considerable if the patient is allowed to consume the diet of the average American, which may contain anywhere from 3 to 6 gms. of sodium daily. Unless this factor is carefully controlled, it is inevitable that the amount of desoxycorticosterone acetate which can be safely employed will be either too little for the patient's needs or so much as to cause a complication from overdosage. We have seen both conditions occur in patients whose diets were not satisfactorily followed after leaving the hospital (5). In one instance, a cardiac complication which nearly ended fatally occurred during the patient's vacation while she was 100 miles from her physician.

To avoid untoward reactions and to take full ad-

*From the Department of Medicine, New York Medical College and the Division of Dietetics, Flower and Fifth Avenue Hospitals, New York, New York.

TABLE II
Soft Diets for 15 Gms Sodium

	Gms	Na	K
Breakfast			
Fruit—1 serving 0.018%	100	0.018	0.183
Cereal—any, 3 tablespoons without added salt (measure before cooking)	200	0.021	0.162
Eggs—2 any style except fried (no added salt)	100	0.140	0.138
Toast—2 slices, white or wholewheat	50	0.197	0.054
Butter—saltfree 2 pats	20	—	0.003
Cream—20% 1/2 cup	100	0.030	0.130
*Cocoa—1 cup	200	0.059	0.436
		0.465	1.116
Lunch			
*Cream soup—for full or light diet, 1 cup	200	0.076	0.586
Cream cheese—1 package	75	0.110	0.040
Or Eggs—2 any style except fried	100	(0.140)	(0.138)
Or Rice in hot milk—1/2 cup cooked rice and 1 cup hot milk	210	(0.113)	(0.220)
Potatoes—mashed or baked 1 medium	150	0.033	0.684
Vegetable puree—1 serving 0.073%	100	0.073	0.310
Bread—2 slices white or wholewheat	50	0.197	0.054
Butter—salt free 2 pats	20	—	0.003
Fruit—1 serving 0.008%	100	0.008	0.210
Or *Sherbert—1 scoop	100	(0.008)	(0.183)
Milk—1 glass	200	0.102	0.286
		0.599	2.173
Dinner			
Minced chicken plus *creamed sauce 2 oz	60	0.108	0.499
Or Sweetbreads plus *creamed sauce 3 oz	90	(0.108)	(0.495)
Or Minced fish—*creamed sauce 2 1/2 oz	75	(0.114)	(0.567)
Potatoes—mashed or baked 1 medium	150	0.033	0.684
Vegetable—0.073% puree 1 cup	100	0.073	0.310
Vegetable—0.016% puree 1/2 cup	100	0.016	0.310
Bread—1 slice white or wholewheat	25	0.098	0.027
Butter—salt free 2 pats	20	—	0.003
*Dessert, choice of	150	0.118	0.212
Soft custard cornstarch pudding			
tapioca pudding rice pudding 2 scoops			
ice cream baked custard blanc mange			
Tea or coffee—1 cup		—	—
		0.446	2.020

For the remaining soft diets use the 15 gram sodium soft diet with the changes indicated below

For 3 gms sodium

Allow 2 slices of rye bread per meal (instead of white bread)

Add 1/2 tsp salt to day's menu

For 4.5 gms sodium

Allow 2 slices of rye bread per meal (instead of white bread)

Add 1 glass of milk at dinner (instead of tea or coffee)

Add 1 tsp. salt to day's menu

Approximate values:

Carb	350
P	90
F	160
Calories	3,000
Vitamins	
A	48,000—49,000
B ₁	950—1,000
C	5,000—5,100
D	500—550
G	1,450—1,600

For 6 gms sodium

Allow 2 slices of rye bread per meal (instead of white bread)

Add 1 1/4 tsp salt to day's menu

For 7.5 gms sodium

Allow 2 slices of rye bread per meal (instead of white bread)

Add 1 glass of milk at dinner instead of tea or coffee

Add 2 1/4 tsp salt to day's menu

For 9 gms sodium

Allow 2 slices of rye bread per meal (instead of white bread)

Add 1 bouillon cube at dinner

Add 2 3/4 tsp salt to day's menu

* See Recipe List

Note:

2 3/4 tsp salt is the largest amount of salt used in the soft diets. It may be distributed as follows:

Breakfast	Lunch	Dinner
Cereal—1/2 tsp	Cream soup—1/2 tsp	Cracked chicken etc—1/4
Eggs—1/4 tsp	Potatoes—1/8 tsp	tsp
Cocoa—1/8 tsp	Eggs or rice in milk—	Potatoes—1/4 tsp
	1/4 tsp	Vegetable puree—1/4 tsp
	Vegetable puree—1/8 tsp	

liquid and light nourishment is served. All food not consumed by the patient is weighed, its salt content calculated, and a corresponding amount of sodium given as Addison's elixir (6) the formula of which is sodium chloride 10 gms, sodium citrate 5 gms, water sufficient to make 1,000 cc and flavoring to taste. In this way, the salt intake is maintained at the desired level throughout each day.

SPECIAL INDICATIONS FOR EACH DIET

In the average patient where no special problem has arisen, it seems advisable to utilize diets containing the average amount of sodium which the normal person would consume, viz those with 3.0, 4.5, and 6.0 gms of sodium respectively. In this connection it must be remembered that the higher the sodium content, the lower the amount of desoxycorticosterone acetate which can be safely used and the less expensive the regimen. On the other hand, dosages of desoxycorticosterone acetate corresponding to an intake of 3 gms of sodium daily (i.e. about 15 mgms) seem to be liked by the patient better than those containing more sodium

and less hormone. Almost invariably the patient "feels more fit" under such conditions.

Diets containing 1.5 gms of sodium have been used solely for investigative purposes, although patients seem to tolerate them well, and in general show satisfactory functional responses. Parenthetically such diets appear to be quite satisfactory for the management of hypertension over short periods of time.

Diets containing 7.5 and 9.0 gms of sodium respectively permit the use of a correspondingly low dose of desoxycorticosterone acetate according to the formula

$$D = \frac{K}{Na}$$

In many instances they are justified for the economies thus effected. It cannot be overemphasized, however, that patients do not feel "quite as fit" as when using more of the hormone and less salt. However we have maintained patients at full-time work satisfactorily for more than a year on the 7.5 gm diet and approximately 6 mgms of desoxycorticosterone acetate daily, and for periods up to six months on the 9.0 gm diet and 5 mgms of desoxycorticosterone acetate daily.

From what has been said it cannot be inferred that

- Cabbage—1 cup
Eggplant— $\frac{1}{2}$ cup or 2 large slices
Lettuce— $\frac{1}{4}$ head
Tomatoes—fresh 1 medium, canned $\frac{1}{2}$ cup
- (3) 0.18% Fruits—100 gm portions
- Stewed rhubarb— $\frac{1}{2}$ cup
Dried apricot—8 halves
Stewed dried peaches— $\frac{1}{3}$ cup
Canned plums—3 plums
Canned cherries— $\frac{1}{3}$ cup
Grapes—1 small bunch
Fresh Peaches—1 med
Fresh pineapple—1 slice $\frac{1}{4}$ " thick
Fresh plums—3 plums
Blueberries— $\frac{1}{2}$ cup
Watermelon E. P.— $\frac{1}{3}$ slice 6" diam
Fresh pears—1 small pear

(4) 0.044% Fruits—100 gm portions

- Stewed prunes—3 prunes
Canned figs—3 figs
Dried figs—4 medium figs
Fresh strawberries— $\frac{3}{4}$ cup
Banana E. P.—1 medium
Cantaloupe E. P.— $\frac{1}{2}$ cup cubes
Fresh cherries— $\frac{3}{4}$ cup
Dates—8 dates
Fresh apricot—2 apricots

(5) 0.073% Vegetables—100 gm portions*

- Beets— $\frac{1}{2}$ cup
Carrots— $\frac{2}{3}$ cup
Turnips— $\frac{1}{2}$ cup
Avocado— $\frac{1}{4}$ large
Broccoli— $\frac{2}{3}$ cup
B. sprouts— $\frac{2}{3}$ cup
Cauliflower—1 cup
Kale— $\frac{3}{4}$ cup

(6) 0.128% Vegetables—50 gm portions to be substituted for 0.073% vegetables when desired*

- Celery—two 7" stalks
1/3 cup cooked
Endive—1 small crown
Lima beans— $\frac{1}{4}$ cup
Dandelion greens— $\frac{1}{2}$ cup

(7) Meats— $\frac{1}{4}$ lb servings—120 gms Na 0.101 K 0.405

- Roast beef—6"x5"x1"
Lamb chop—1 large
Roast lamb—2 slices 4"x4"x $\frac{1}{2}$ "
Roast mutton—2 slices 3"x4"x1"
Beefsteak—5"x4"x2"
Roast veal—4"x5"x1"
Veal cutlets—1 large
Beef patties—2 small
Chicken—broiled 1/3 broiler roast 2 slices 4"x2"x $\frac{3}{4}$ "
Turkey—2 slices 4"x3"x $\frac{1}{3}$ "

(8) Fish—1/3 lb serving—150 gms Na 0.000 K 0.240

- Haddock—5"x4"x1"
Flounder—5"x4"x1"
Mackerel—4"x4"x2"
Trout—3"x4"x $\frac{1}{2}$ "
Halibut—4"x4"x1"
White fish—4"x4"x $\frac{1}{2}$ "
Blue fish—3"x5"x2"

* Measure vegetables after cooking unless otherwise plainly noted

TABLE V

Recipes

Na 0.017 K 0.098

Cereal Gruel
1/3 cup cereal
1 $\frac{1}{2}$ cups water

Add cereal to boiling water. Boil 10 minutes, and cook in double boiler $\frac{1}{2}$ hour. Strain and serve with cream.

Chocolate Blanc Mince* Na 0.109 K 0.365

$\frac{1}{2}$ cup milk 1 tbs cornstarch
1 tbs sugar 1 tbs cocoa
Few drops vanilla 1 egg white

Blend cornstarch and equal parts milk. Heat remainder of milk in double boiler. Add cocoa, sugar, and then moistened cornstarch. Cook 20 minutes in double boiler. Remove from heat, add vanilla and fold in beaten egg white. Chill.

* For plain blanc mince, omit cocoa.

Chocolate Frosting Na 0.156, K 0.656

1 glass milk 1 scoop ice cream
1 heaping tbs cocoa

Cocoa (for liquid or soft diets) Na 0.059 K 0.436, 200 gms

$\frac{1}{2}$ cup milk 1 heaping tbs cocoa
Sugar as desired $\frac{1}{4}$ cup water

$\frac{1}{4}$ cup cream (20%)

Cocoa (for full or light diets)

1 cup milk
Sugar as desired
1 heaping tbs, cocoa

Cornstarch Pudding

Na 0.112, K 0.173

1 tbs cornstarch A few drops vanilla
 $\frac{1}{2}$ tbs cold water 1 egg yolk
1 tbs sugar $\frac{1}{2}$ cup scalded milk

Mix cornstarch in cold water and pour into hot milk. Cook until it thickens. Beat egg yolk, add the sugar and pour the hot mixture over them. Cook in double boiler until mixture thickens.

Cream Sauce

Na 0.057, K 0.297

$\frac{1}{2}$ cup milk 1 tbs flour
2 squares salt-free butter

Cream Soup (for liquid or soft diets) Na 0.118, K 0.571

1 cup milk $\frac{1}{2}$ cup 0.016% vegetable puree
1 tsp flour 1 square salt-free butter
Melt butter. Add flour. Pour milk slowly into butter-and-flour mixture. Add vegetable puree.

Cream Soup (for light or full diets)

$\frac{2}{3}$ cup milk
1 tsp flour
 $\frac{1}{4}$ cup 0.016% vegetable puree
1 square salt-free butter

Soft Custard

Na 0.118, K 0.306

1 cup scalded milk 1 egg yolk
2 tbs sugar 2 or 3 drops vanilla

Place egg yolk and sugar in top of double boiler and stir until blended. Stir in scalded milk slowly and cook until custard coats a metal spoon.

Eggnog, Chocolate*

Na 0.180, K 0.485

1 cup milk Vanilla
1 egg 1 tbs cocoa
2 tsp sugar

Add sugar, milk and vanilla to a well beaten egg. Dissolve cocoa in a small amount of the milk and boil for 1 minute. Pour both mixtures into shaker and shake well with ice.

* For plain eggnog omit cocoa.

Orange Orange

Na 0.096, K 0.468

1 egg 1 glass orange juice
2 tsp sugar $\frac{1}{2}$ tsp lemon juice
1 tbs cream

Beat egg yolk. Add half the sugar. Then add gradually the orange and lemon juice. Add the cream and fold in stiffly beaten egg white to which has been added the remainder of the sugar.

of a single vitamin the only aspect of the problem which would seem to make further investigation desirable. Many national diets, as well as certain therapeutic diets, contain a preponderance of carbohydrate, fat or protein. Could it be that such diets might affect the body's needs for nutrients other than the vitamins of the B-complex?

The existence of a relationship between the amount of ascorbic acid and the fat carbohydrate and protein content of the diet has not been definitely established. The limited studies on this relationship lack uniformity in methods of procedure and are controversial as to their results. Since a slight ascorbic acid deficiency is wide-spread there is a practical need for studying this relationship.

The four papers, all of which appeared in 1936, dealing with the effect of high carbohydrate, fat and protein diets upon the ascorbic acid excretion of man were not in agreement as to the conclusions drawn. Chakraborty and Roy (6) reported that a high protein diet increased the body's need for ascorbic acid since in two male subjects they found the indolphenol-reducing properties of the urine was lower on the high carbohydrate diet of the Bengali than when a diet containing larger amounts of protein either as meat or as casein, was consumed. This same high reducing power of the urine was also reported when large amounts of butter were added to the diet. Alimad (7) using himself as a subject partly corroborated these findings reporting that a high meat diet increased the body's excretion of ascorbic acid. On the other hand, Chopra and Roy (8) in a study of three individuals ingesting 240 grams of fat a day found no increase in the indolphenol titer of the urine although the acetone bodies in the urine did increase. Hememann (9) concluded from his work that the increased reducing capacity of the urine found by other workers when diets high in protein and fat were ingested came from reducing substances other than ascorbic acid. The experimental procedure used in these studies was not uniform and the diet was not carefully controlled with the exception of that of Hememann. In no case were the diets balanced in respect to the other nutrients. This paper presents the results of the influence which controlled and balanced diets had upon the excretion of ascorbic acid of eight women engaged in academic work.

EXPERIMENTAL PROCEDURE

A micro-method similar to that of Birch and Harris (10) was used in testing for ascorbic acid. The dye was standardized against pure crystalline ascorbic acid, and was made up fresh at short intervals and kept in a dark bottle in the refrigerator.

After comparing the amounts of ascorbic acid obtained when titrating the urine as voided with those of the pooled 24 hour samples to which had been added meta-phosphoric acid to stabilize the ascorbic acid as advocated by Musulin and King (11), the latter method was adopted and used throughout the experiment. As a further precaution against loss of ascorbic acid the urine was kept in dark bottles and in a cold place, usually in the refrigerator.

The experiment as first planned included four diets, a "normal" a high carbohydrate a high fat, and a high protein diet. These diets were lacking only in ascorbic acid, otherwise meeting or exceeding requirements for the other nutrients as prescribed by accepted dietetic practice of that time (the thiamin and riboflavin are somewhat lower than that now recommended by the National Research Council). The exception to this was the high fat diet in which the iron and vitamins of the B-complex were somewhat low. With the vitamins A and D the tendency was to exceed the average requirement since most of the subjects had been taking a concentrate of these two vitamins and were permitted to continue during the experimental period. The proportion of fat carbohydrate, and protein furnished by each diet used may be seen in Table I.

The amount and variety of the food in each diet was carefully controlled and measured and the same foods were eaten each day through the experimental period. During the preliminary experiment the food was measured, in the case of the six subsequent subjects all the food was weighed, prepared and eaten in the laboratory. The foods which were common to all the diets were whole cereal, beef eggs raisins, butter and milk. From time to time the milk was tested for ascorbic acid and was always found to be free of this vitamin. For the high carbohydrate diet, dark corn syrup brown sugar, increased amounts of cereal and raisins were added to increase the carbohydrate. For the high fat diet most of the calories came from butter cream and mayonnaise. Protein was increased in the high protein diet with eggs, dried milk, cheese and nuts rather than with meat which Hememann (9) believed increased the indol-reducing capacity of the urine by substances other than ascorbic acid. The amount of meat of all four diets used in these experiments was kept constant eliminating the possibilities of reducing bodies from this source entering into the interpretation of the results. Harris (12) considers this effect of reducing substances other than ascorbic acid, of more theoretical than practical importance since such reduction takes place more slowly than does that of ascorbic acid.

TABLE I

Showing the Distribution of Carbohydrate Fat and Protein in the Diets Used

Diet	Carbohydrate %	Fat %	Protein %
'Normal'	48	38.5	13.4
High Carbo	67	21	12
High Fat	27	62	11
High Protein	37.2	35.9	26.7

Two periods were planned for each diet since it seemed wise to determine the effect of a predominance of each of these nutrients, carbohydrate fat and protein upon ascorbic acid excretion of the body when the diet was lacking in ascorbic acid and when known amounts of ascorbic acid were being administered. The first period on each diet was a "depletion" or "fore-period" during which time no ascorbic acid was taken.

With the first two subjects used in these experiments a plateau appeared to be reached at the end of the fifth

TABLE IV

Showing the 'Basal Level' of Ascorbic Acid Excretion During Depletion

Subject	"Normal" Diet		High Protein Diet		% Variation from 'Normal'
	Days Run	"Basal Level" Ascorbic Acid Mg	Days Run	"Basal Level" Ascorbic Acid Mg	
IP*	10	11.39	8.3	16.42+	+44.1
AB*	10	14.98	7.5	17.09#	+14.0
AP	9	25.39	9	23.82	-6.2
GM	9	27.99	8	32.32	+15.46
TH	9	18.38	9	18.74	+0.2
JW	9	18.48	9	16.28	-11.9
MT	7	19.42	9	16.44	-15.3
FW	9	18.01	9	15.23	-15.43
Average	9	19.25	8.6	19.54	+1.5

* Subjects in First series

+ Average two depletion periods

Average three depletion periods

When the "basal levels" of ascorbic acid excretion of the eight subjects were averaged for the two diets they differed only by a plus 1.5%. For the second series the greatest positive difference between the ascorbic acid excretion on the "normal" diet and that excreted on the high protein diet was 15.6% and the greatest negative difference in this series was 15.4%. Since the day to day variation in the ascorbic acid excretion might vary by as much as 20% even after the period of relative stability had been reached this variation between the average of the two diets under considera-

tion on the high protein diet than were required when the 'normal' diet was eaten. The fifth subject, AP, required the same number of days to become saturated regardless of the diet. When this subject's record was examined it was found that contrary to instructions during the saturation period on the high protein diet she had taken aspirin for a headache. Samuels et al (14) report that in the guinea pig and rat salicylates increase the urinary excretion of ascorbic acid. This confirmed the earlier observation by Daniels and Eversen (15) on children. Hence the

TABLE V

Showing Difference in Saturation Time on Diets Used

Subject	Normal Diet			High Protein Diet		
	Ingested Ascorbic Acid Mgs daily	Days run	Day of saturation	Ingested Ascorbic Acid Mgs daily	Days run	Day of saturation
IP	100	7	(3)*	200	5	4
AB	100	7	(4)*	200	6	5
AP	200	5	5	200	6	5
GM	200	6	---	200	5	-
TH	200	6	4	200	6	---
JW	200	5	4	200	6	5
MT	200	6	---	200	6	5
FW	200	5	4	200	6	5

* On the high fat and carbohydrate diets plus 200 mg ascorbic acid saturation occurred on the 3rd and 4th days

tion would hardly seem significant. This study, then using a carefully controlled and balanced diet, would seem to present further evidence to corroborate those investigators who find that the excretion of ascorbic acid is not increased by the ingestion of a high protein diet.

That the ascorbic acid excretion of the body is not accelerated by a high protein diet does not necessarily mean that ascorbic acid is not involved in protein metabolism or that the body's need for this vitamin has not been increased by feeding high protein.

The results of the saturation studies indicate that the ingestion of a high protein diet seems to have a tendency to increase somewhat the body's need of ascorbic acid. When the results of the saturation period are considered (Table V) it is found that of the six subjects saturated, four took one day longer or 200 mg more ascorbic acid were needed for satu-

aspirin in this case might easily have accounted for the apparent earlier saturation of this subject on the high protein diet. The sixth subject, TH, did not become saturated by the sixth day on the high protein diet though saturation occurred on the "normal diet" in four days, or on 800 mgs of ascorbic acid. The seventh subject, GM, was not saturated on either diet before the experiment was terminated. The eighth subject MT, did not saturate during the six days she was ingesting the 'normal' diet but did become saturated by the fifth day when eating the high protein diet. For this no explanation can be offered except perhaps that she had a good deal of difficulty at first in adapting herself to the experimental diet.

If it is true that the body has a greater need for ascorbic acid when the protein is high in the diet, it might have been expected that the "basal level" of excretion of the acid would be lower on the high pro-

Some Effects of Diets Rich in the Glycerides of Saturated Fatty Acids on Intestinal Elimination* II.

By

HELEN L. WIKOFF, Ph.D. JEAN F. CAUL, Ph.D.

and

BERNARD H. MARKS, B.A.

COLUMBUS, OHIO

IN a previous investigation directed by one of us (1) a study of the effects of high fat diets on intestinal elimination was begun. This research was prompted by some seemingly contradictory effects reported by human subjects (2) who had been put on diets containing large amounts of fried foods, pastries and other fat-rich foods. Some of these patients experienced diarrhea, others were constipated and still others developed no intestinal symptoms at all when on the same high fat diet.

In two groups of eight subjects each it was found that there was considerable individual variation in the presence or absence of constipation as reported by the subject himself. With some, the slightest change in consistency of the feces or irregularity of movements was reported as constipation. There was much more agreement on reported diarrhea, that term being reserved for frequent watery stools. The subject was quite sure when he had diarrhea although he might not have been quite so sure when he was constipated.

Because of this experience we decided to feed high fat diets to animals. Because the white rat thrives on relatively unvaried diets it was selected as the laboratory animal for our first series of experiments.

Two facts were discovered from the experimental work with rats: (1) Constipation can be brought on when large amounts of certain fats are fed to rats; (2) Rats do not develop diarrhea even when red castor oil and so cannot be used to determine laxative effects of fats or oils.

Because the dog is said (3) to resemble man in his nutritional requirements and in his digestion and absorption of food it was decided to undertake further studies of the effects of high fat diets on intestinal elimination with dogs as the experimental subjects. Since the work previously carried out with rats had indicated that not all fats behave alike we decided to synthesize simple triglycerides for feeding in order to determine exactly which fatty acids might be responsible for any unusual reactions produced.

PROCEDURE

Four healthy male dogs were used as subjects for the feeding experiments. Dog X, full grown but age unknown, was a thirty-pound mongrel (part spaniel) which before being used as an experimental subject had been wormed and thoroughly conditioned at The Ohio State University Veterinary Clinic. Dog C, exact age not known, was a twenty-three pound mongrel

(hound and collie mixture) obtained about a year prior to this work. Dogs R and W weighing seventeen pounds and thirteen pounds respectively, were smooth-haired fox terriers of the same litter. They were about sixteen months old at the beginning of this experiment and had been pronounced healthy by veterinarians who examined them thoroughly before the feeding experiments were begun.

During the experiments the dogs were kept out-of-doors in separate pens or indoors in separate cages from which they were removed for periods of exercise. All were fed once a day and at the same time. Dog X was maintained on Purina Laboratory Chow* except when the high fat diets were being tested. Dogs C, W, and R were each fed the contents of a one-pound can of Pard** per day.

*Chemical Analysis Purina Dog Chow (New Formula)	
Protein	23.00
Fat	6.50
Fiber	3.75
Ash	8.25
Nitrogen free extract	50.00
Calcium	1.85
Phosphorus	1.20
Iron	.017
Copper	.0007
Chlorine	.60
Sodium	.40
Potassium	.60
Carotene	1700 I.U./lb
Vitamin A	8000 I.U./lb
Thiamin	5000 International Units/lb
(Vitamin B)	1.82 mg./lb
Vitamin D	454 International units per pound
Riboflavin	1800 micrograms per pound

**Chemical Analysis of Pard Dog Food (Switt & Company manufacturers)

Protein (minimum)	10.50%
Fat (minimum)	2.50%
Nitrogen free extract (minimum)	9.00%
Crude Fiber (maximum)	1.00%

Ingredients

Meat	Tomato puree
Meat by-products	Edible bone
Wheat	Salt
Soy flour	Cod liver oil
Barley	Water
Dried skim milk	

Approximate caloric value one pound Pard 450

When added fat was to be introduced into the diet, the contents of a can of Pard (454 gm.) were thoroughly mixed with the calculated amount of triglyceride (90.6 gm. for a 20% diet) in a mortar. The dog was then allowed to eat directly from the mortar in

*From the Department of Physiological Chemistry, The Ohio State University College of Medicine. Aided by a grant from the Comby Research Fund of The Ohio State University.

DISCUSSION AND RESULTS

Because constipation had been produced when diets containing twenty percent added coconut butter or twenty percent hawberry tallow were fed to rats, (1) tristearin and tripalmitin, triglycerides prepared from the fatty acids most characteristic of these two fats were the first of the pure glycerides added to the standard diet fed to the dogs. After such feedings there was definite evidence of constipation in all of the dogs. The stools were dry and friable and consisted of short segments containing specks of solid white material. Normal dog stools resemble those of humans. They are soft but well-formed, sausage shaped and have few or no indications of haustral contractions.

Table I contains the analytical data for the fecal material collected on the third day after feeding of the various high fat diets. Inspection shows that when either tripalmitin or tristearin was added to the diet the moisture content of the feces diminished appreciably. While there was considerable individual variation among the three dogs nevertheless the moisture content of the feces, in all cases, was much lower than the normal value. Individual decreases in moisture content were greater after the addition of tristearin to the diet than after tripalmitin.

The lipid content of the feces was greatly increased when either twenty percent tristearin or twenty percent tripalmitin was added to the diet of the experimental dogs. This might have been expected from the appearance of specks of solid white material. There was a much greater increase in the neutral fat fraction than the soap fat but the soap fats were somewhat more unsaturated than the neutral fats. The high lipid content of the feces after tristearin and tripalmitin feedings seems to agree with certain statements of Hilditch (6) 'so long as the ingested fat is liquid at the temperature of the digestive tract, the specific nature of the fatty acids present is largely immaterial so far as power of assimilation and utilization is concerned. Fats of higher melting points are however dealt with difficultly and are frequently excreted unchanged. When a normal healthy animal is fed with fats of high melting point these are however excreted for the most part unchanged.'

The melting points of the tristearin (66.5°C uncorr) and of the tripalmitin (59.5°C uncorr) were decidedly above the temperature of the digestive tract (about 37°C). The excretion of feces high in fat content following such feedings is thus in accord with the ideas of Hilditch, who states that digestibility declines only when the ingested fat approaches a melting point of about $48\text{--}50^{\circ}\text{C}$.

Because some of the tributyrin from our previous experiments with rats was still on hand, we next tried to feed a meal of Pard to which twenty per cent tributyrin (solidification point— 78°C) had been added. However all of the dogs refused to eat the food containing either twenty or ten percent added tributyrin. Finally, it was decided to feed some of the tributyrin to Dog X by means of a stomach tube. Twenty-five cc of tributyrin (equivalent to about twenty-five percent

of the fat which was added to the regular diet in the preparation of the previous twenty percent diets) were introduced by a stomach tube, after which the dog was permitted to eat one-fourth pound of Pard. Defecation took place after five minutes while within thirty-five minutes the Pard was vomited. The first part of the feces which appeared to be normal was probably the residue from the meal of the previous evening. This soon was followed by yellow, stringy mucous material which was collected and analyzed (Sample I, Table II). About two hours later there was a second defecation of material (Sample II, Table II) much the same in appearance as Sample I except that only globules were definitely noticeable. A part of the material from each of these evacuations was extracted with neutral isopropyl ether and the extract saved for examination. A small amount of the stringy material when treated with Molisch and Buret reagents gave positive tests indicating the presence of glycoprotein, probably mucus.

Because of these rather unexpected results, Dog X was maintained on a meat-free (Purina Chow) diet until daily fecal suspensions consistently gave negative benzidine reactions for blood. Then twenty-five cc of tributyrin were again administered by stomach tube sixteen hours after the meal. This time no food was given afterwards. One-half hour after the forced feeding of the glyceride, the dog passed a formless fecal mass of oily consistency. Four hours later a mucous, oily yellow sample (III) was expelled and soon afterwards a more fluid mucous sample (IV) showing only globules was collected. Samples III and IV were saved and analyzed in the same manner as the feces collected after the previous feeding.

TABLE II

Analytical Data from Fecal Material Collected After the Forced Feeding of 25 cc of Tributyrin to Dog X

Sample	Benzidine Reaction	Sapon No Isopropyl Ether 1 ccr	Sapon No Tributyrin	Acid No Isopropyl Ether 1 ccr	Molisch Test	Buret Test
I	—	562.1	557.7	—	+	+
II	—	—	—	76.9	+	+
III	+	419.2	—	131.6	+	+
IV	+	445.7	—	231.8	+	+

The drastic effect of tributyrin with respect to the alimentary tract is apparent from these data. It is regrettable that Samples I and II were too small to permit both a saponification and an acid number to be run on each. However, the close agreement of the saponification number of Sample I with the theoretical value for tributyrin suggests that probably the oily material present in the feces passed first was mainly tributyrin. The material which remained in the digestive tract for longer periods of time was hydrolyzed to greater extents as indicated by the acid numbers.

Since it was impossible to persuade the dogs to eat diets containing appreciable amounts of added tributyrin an attempt was made to persuade them to eat

12 Tributyrin having the most violent action of any of the fats fed caused diarrhea in Dog C when as little as two tenths of one percent was added to the standard food. Furthermore, Dog C would not eat all of the usual daily ration of a pound of Purina after the addition of two-tenths of one percent tributyrin.

CONCLUSIONS

The effect of a high fat diet on intestinal elimination depends, at least partially, on the chemical composition of the fat fed. By feeding dogs pure simple triglycerides of saturated fatty acids we have produced three different intestinal conditions. These include normal elimination after a diet consisting of standard dog food to which as much as twenty percent trimyristin had been added; constipation after twenty percent additions of tripalmitin or tristearin to the standard diet; and laxative effects after the addition of simple triglycerides of some of the saturated fatty acids of twelve or less carbon atoms (lauric, capric, caprylic, caproic, butyric acid) the amounts added varying from twenty to two-tenths per cent. The cathartic action of the simple triglycerides increases as the number of carbon atoms in the component saturated acid decreases.

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Notes On Nutrition

Food is continually essential to an army. Research must continue while no let up is permitted in the delivery of foods. Food is in greater demand than ever before because soldiers eat more, civilians have more money to buy food and lend-lease takes food. The army has studiously managed to curtail the use of coffee, tea, fats, canned goods and butter. Food has been increased by exploitation of surplus crops, expansion of processing industries and the use of local resources abroad. Shipping space is increased by reduction of bulk as by dehydration. Compression will be used to squeeze even the air out of foods. Soon one ship will carry what formerly required sixteen ships. The effects of temperature, altitude and humidity variations have to be known in such matters as packaging and proper cooking. Specialized troops as well as varying geophysical conditions are reflected in food requirements. For 20 years prior to the war research had been done on food mobilization, so that we were not unprepared. The palatability of dehydrated foods is a problem now being attacked. The wartime fatigue of the soldier is directly related to military nutrition. It is not enough to feed a soldier—he must be fed in a way to provide him with a maximum of energy and morale. Food is valuable munition. What we learn in feeding an army will have good effects later on civilization nutrition. (Col. Georges F. Doriot, Off. of Q. M. G.)

New fat soluble vitamin reported. A fraction of raw cream—which in its concentrated state is a pale yellow oil—was found curative in very small doses for a disease of guinea pigs characterized by stiffness of the wrists, and one which develops when guinea pigs are fed a good diet of skimmed milk, skim milk powder, carotene, iron, copper, and orange juice over a period of one month. The identity of this new vitamin is not certain, and further work will be required to show that it is actually a food essential for the species used. (Arch. Biochem., 1, 373, 1943)

Iron loss by blood donors. Iron supplement ought to be given to repeating blood donors, because there is a loss of iron of 3 mg. a day in cases where the donor gives 1 pint of blood 5 times a year, and theoretically the normal diet will not make good such a loss. Chinese blood donors subsisting on inadequate diets actually show the occasional development of a hypochromic anemia. Hemoglobin regeneration has been shown to occur 8 times as fast when the individual is given 12 grains of ferrous sulphate per day. Iron deficiency may develop in regular donors if their diets are not good. Iron stimulates hemoglobin regeneration after blood donation, but this effect lessens after repeated donations. Repeated donations do not produce bone marrow exhaustion. Foods rich in iron and protein are important in the diet of donors. Copper and Vitamin B Complex are of importance also. 400

(J. Am. Dietet. Assn. 19, 336, 1943)

Nutritive value of enriched white flour and bread. The enrichment of flour with thiamine was undertaken on theoretical grounds but now it has been proved that the enrichment actually does away with signs and symptoms of deficiency. The ingestion of a diet which provided only 0.22 mg. of thiamine per 1000 calories results after some months in mild thiamine deficiency, whereas the substitution of enriched flour (white or whole wheat) by raising the thiamine intake to 0.45 mg. per 1000 calories, in large measure prevents the deficiency. The clinical experiments suggested that the enrichment of flour with thiamine goes a long way toward correcting the deficiency of thiamine that is apt to occur in the usual selection of foods by the American people. (I. A. M. A., 121, 943, 1943)

Vitamin synthesis in ruminants. Feeding experiments on cows with fistulas from which the rumen could be collected and analyzed indicated that riboflavin was synthesized in the rumen apparently by the action of dominant bacterial flora, viz. a bacterium of the genus *Flavobacterium*. The higher the carbohydrate content of the feed the higher the amount of riboflavin synthesized; hence ground corn was a factor favorable to this synthesis. Some support and some deny that thiamine also can be synthesized in the cow's rumen. (J. Nutrition, 25, 207, 1943)

Nutrition and resistance to infection. Although it was found that biotin deficient chicks and ducks showed a decreased resistance to infestation by mite-like parasites, it was shown by another investigator that poorly fed mice showed increased resistance to infection by the virus of murine poliomyelitis. Possibly parasitism may be so complete that only a well nurtured cell will suffice as a host. (Science, 97, 206, 207, 1943)

The Metabolism of Vitamin A. When the liver contains plenty of Vitamin A there is no correlation between liver and serum concentrations of this vitamin but when the liver supply is low, the serum and the liver levels tend to move together. High blood levels following ingestion of large doses of vitamin tend to be maintained over a long period after discontinuance of the excessive intake. This suggested that liver saturation had reached a stage beyond which it could not take up any more of the vitamin. There has been found a relationship between the total lipid and the Vitamin A of the serum, the blood lipids acting as a vehicle for the vitamin, tending to hold it in the blood. It is suggested that Vitamin A is concerned with lipid metabolism. Perhaps the lipid response to administration of Vitamin A can be developed into a practical physiological test of Vitamin A deficiency in the human subject. (Bull. Johns Hopkins Hosp. 71, 253, 1942)

Public Health approach to nutrition. Some public health nutrition surveys are in progress; the first pub-

lished part of which deals with caloric intake. It was found in a Tennessee community of 1152, of which 91 per cent were examined that the caloric intake of a large proportion of individuals was much lower than 3000 cal per day. Judging from the fact that these people stayed well, worked and held their weight, it seems possible that the recommended caloric allowances of 3000 cal per diem of the Food and Nutrition Board may be set too high. (*Am J Pub Health*, 32, 1371 1942; *Ibid*, 33 58 1943)

Dietary fat and Vitamin A absorption Some rat feeding experiments show that while Vitamin A absorption is aided by dietary fat, its utilization after assimilation has occurred is independent of the fat. Other experiments with hens do not bear out this idea. More work on this difficult problem is needed. (*J Nutrition*, 23, 335 1942) (*J Nutrition* 24 199, 1942)

Pathological changes in Vitamin C deficiency Ascorbic acid has a function in the activity of cells forming the protein substance collagen. It appears also that ascorbic acid is concerned in the metabolism of tyrosine and phenylalanine. In guinea pigs deprived of ascorbic acid, pathological changes occur in the parenchymatous cells of the liver and in the proximal convoluted tubules of the kidney. This is suggestive since the liver is concerned in protein metabolism. The primary histological effect of scurvy is the cessation of osteoblastic activity. (*Arch Path* 35, 579 1943)

The reliability of food tables A remarkable correspondence between actual values for food items and their value as calculated from food tables was found to exist except in the case of iron and calcium. Additional iron may come from curry powder and especially from cooking in iron dishes or cutting or grinding with iron utensils so that much of the iron in the human system has come from utensils. Much calcium is gained from water, especially in areas where hard water is used. (*Lancet*, 1 230 1943)

Vitamin E and muscle physiology Lack of Vitamin E produces muscle paralysis in suckling rats and many other animals. Such paralysis is prevented and cured by the administration of tocopherol. The dystrophic muscle so produced by lack of Vitamin E uses much more oxygen than normal. Tocopherol by its presence hinders chemical changes within the succinioxidase system, so that in its absence the oxidative process runs riot. The idea that a vitamin may act as an inhibiting principle in contrast to the positive catalytic action of some other vitamins is an interesting suggestion in the field of biological oxidation.

Foods that disagree with healthy people In a study of normal people it was found that raw onion was the chief food which disagreed with them, for approximately 25 per cent of 1000 healthy persons reacted to onions with four or more symptoms (belching, nausea, headache, distention, regurgitation, vomiting, pain, urticaria). Other offending foods in the order of their importance were,—radishes and cooked cabbage, beans, and many others in much smaller numbers. Cooking increases the bad effects of cabbage but greatly improves those of onions. Starting the cooking in hot water and light cooking were found to favor the

agreeability of the foods. (*J Am Dietet Assn*, 15 24, 1939), (*Ibid*, 18, 815, 1942)

The choline content of animal and plant products Among the richest sources of choline are egg yolk, visceral organs of animals and heart and nerve tissues. Green leafy vegetables and vegetable legumes are better sources than grain seeds or vegetable root crops. Choline now is accepted as an important dietary factor. (*J Nutrition* 25 441 1943)

Avidin and ovarian function Avidin, a protein substance found in egg white combines with biotin in the intestinal tract and causes biotin deficiency if fed in large enough amounts. Avidin is formed and secreted in the oviduct of fowl, when the fowl is laying, but not otherwise, and therefore depends ultimately on the reproductive function of the ovary. Avidin reproduction can be stimulated in immature fowl by injections of stilbestrol followed by progesterone. (*Proc Soc Exp Biol*, 52, 140, 1943)

Myocardial necrosis in thiamine deficiency The human disorder beriberi is classically known as consisting of two main forms—the 'wet' type and the 'dry'. The former is characterized by edema and signs of heart failure. The 'dry' form is marked by paralytic symptoms.

Pathologic observations in human beriberi have not been satisfactory. In the 'wet' type particularly, pathologic studies have for the most part been limited to gross examination of the heart, and few detailed microscopic studies have been made. Wenckebach (*Das Beriberi Herz, Julius Springer Berlin (1934)*) described 'hydropic' degeneration of the myocardial fibers, but Weiss and Wilkins (*Ann Int Med* 11, 104 (1937-38)) found the same change in other types of heart disease as well, and Wilkins and Cullen (*J Clin Invest* 12 1063 (1933)) found an increase in the water content of the myocardium of both ventricles in the hearts of patients dying of congestive failure of various types.

Attempts to reproduce the syndrome of beriberi have heretofore been made largely by feeding animals autoclaved yeast. Such studies have been made chiefly in pigeons but other animals including dogs, rats, and pigs have been studied to some extent. In only a few of the experiments reported have specific lesions of the myocardium been described, and these reports have appeared only recently. Swank (*J Exp Med* 71, 683 (1940)) observed scattered foci of necrotic muscle fibers in pigeons, and this worker together with Porter and Yeomans (*Am Heart J* 22 154 (1941)) reported small scattered foci of necrotic muscle fibers in 3 out of 14 dogs. Van Etten, Ellis, and Madsen (*J Nutrition* 20, 607 (1940)) found scattered areas of "atrophy and necrosis" of heart muscle fibers in 7 pigs fed a diet supplemented with sulfite-treated liver and whey. It is noteworthy also that in foxes dying of Chastek paralysis, a disorder which has been attributed to thiamine deficiency, Evans, Carson and Green (*Am J Path* 18, 79 (1942)) also described areas of necrosis of myocardial fibers.

Much more pronounced changes in the heart than have been described are reported in pigs by Folhs,

Miller, Wintrobe and Stem (*Am J Path* 19, 341 (1913)). It is to be noted that these workers did not depend on autoclaved yeast for the production of a deficient diet because as they point out autoclaving may destroy more than thiamine. They gave as the only source of the Vitamin B-complex a mixture of crystalline vitamins which included riboflavin, nicotinic acid, pyridoxine, choline and calcium pantothenate. Three animals were given no thiamine whatever and 3 others received 10 micrograms of thiamine hydrochloride per kilogram of body weight per day. A third group of animals received no crystalline vitamins, but were fed 1.5 g of desiccated whole liver per kilogram of body weight per day.

Striking changes in the cardiovascular system developed. Four animals which had shown nothing more than some impairment of appetite and of growth, died quite unexpectedly. Two animals were observed to develop labored breathing and cyanosis which were made much worse by exercise. One of these animals died after induced exercise. Three animals were killed.

In all the animals except those killed, pronounced changes in the myocardium were observed. These consisted of areas of focal or diffuse necrosis, some of which were infiltrated by leucocytes and in the more chronic cases, were replaced by connective tissue cells so that scars resulted. The lesions in one instance were so great that they could be detected grossly. The hearts showed well pronounced dilatation, although the evidence of actual muscular hypertrophy was not conclusive. In a pig which died early in the experiment lesions were confined to the auricles, but in those dying later lesions were noted both in the auricles and in the ventricles. In no instances were pathologic changes found in the ventricles when they were lacking in the auricles. This indication that the auricles may be more sensitive to thiamine deficiency than the ventricles is of interest in relation to the observation by Muir, Weiss and Hastings (*J Biol Chem* 129, 305 (1939)) who noted that there was a reduction from normal in the oxygen consumption of the auricular muscle *in vitro* in thiamine deficient rats while that of the ventricles remained unchanged. In the animals which were killed no myocardial lesions were observed. These animals had been receiving thiamine in doses sufficient to reduce the pyruvic acid of the blood to normal levels for the preceding thirty to forty-five days.

The myocardiums of 45 pigs which had died of deficiencies other than thiamine or which had received all of the crystalline vitamins of the B group were examined and failed to show the myocardial necrosis described in thiamine-deficient animals. It is to be noted that a number of these animals had failed to grow normally and that two were pigs whose food had been purposely restricted in order to study the effect of chronic inanition on the tissues. The myocardial lesions cannot therefore be attributed simply to inanition.

This report brings convincing evidence of the important role of thiamine in maintaining the integrity of the heart muscle. In view of the well recognized role of thiamine in carbohydrate metabolism the observa-

tions recorded are however not surprising. They show clearly how a biochemical defect may lead to profound histologic changes.

It will be necessary to examine carefully the hearts of patients dying as the result of nutritional deficiency in order to see whether lesions similar to those observed in pigs will be found in man. As already stated the studies in man hitherto recorded have scarcely been adequate enough to indicate whether similar lesions are likely to be found. It is to be noted that pathologists have observed and reported from time to time cases of unexplained myocarditis associated with heart failure in which the changes were strikingly similar to those now reported in thiamine deficiency. It will be interesting to see whether directed observations will reveal evidence of thiamine deficiency in some of the cases of unexplained myocarditis.

It is also to be noted that Folks, Miller, Wintrobe, and Stem were unable to find changes in the nervous system in any of the animals and did not find evidence of degeneration of the vagus nerves. Degeneration of the vagus nerves was at one time considered to be a cause of the cardiac manifestations of human beriberi. The paralysis observed in beriberi has also been attributed to thiamine deficiency. Views as to whether thiamine deficiency is responsible for nerve degeneration in man have been largely gained by inference from animal experimentation. Questions of species differences, time for development of the deficiency as well as the type of diet all appear to be factors leading to differences of opinion in this matter (*Nutrition Reviews* 1, 252 (1943)). Certainly on the basis of present knowledge concerning the distribution of vitamins in food, beriberi would be expected to be a multiple deficiency syndrome resulting from the lack of more than one vitamin. While it appears that the cardiac manifestations of this disorder may be due to lack of thiamine other symptoms may be due to deficiencies in other substances.

More about Nutrition in Industry. In a round table discussion of many matters brought up at the 5th Annual Congress on Industrial Health in Chicago in January, the remarks of Wilder regarding carbohydrate intake are of clinical interest. The tendency to develop low blood sugar values between meals may be a reason for consumption of carbohydrate-rich foods at those times. While this habit may at first produce some feeling of relief it ultimately may lead to an increased sensitivity to fatigue. In well recognized cases of hypoglycemia the preferred method of treatment is to place the patient on a high protein, high fat diet with restriction of carbohydrate, particularly sugar. A good breakfast and lunch of this type will do much to prevent this type of weakness about 11 A. M. and 4 P. M. (*J A M A* 121, 906 (1943)).

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Editorial

MONISM IN MEDICINE?

THE work of the psychosomatic movement was not undertaken to buttress the theory of monism. Indeed, like other groups of physicians they are less interested in philosophy than in finding a mode of practice that gets patients better. Yet when we are asked to think of man not as a body *and* a psyche, but as a unit and a single whole the ancient problem of duality versus monism is emphasized. We are so accustomed to the analytic approach that we find it difficult to think in terms of *wholeness*. Is man actually a whole or an assembly of parts? Such intangibles as pertains to the consciousness,—cognition, will, affection, patterns of conduct, social reactions, and the like—seem to be rather unrelated to the substantial body of tissues which has formed the chief object of medical research. It would be quite impossible on scientific grounds we feel, to show that the psyche and the body are merely aspects of one whole. True enough the emotions, which appear to be about half mental and half physical do provide a link of a sort, and it is this link which seems to furnish the only logical ground for assuming that man may be an entity. It has been found that any method of toning down the emotions and conferring emotional stability upon those not possessing it results in the disappearance of many somatic symptoms. Thus psychotherapy (either of the minor variety (cheerfulness, persuasion, suggestion) or of the major kind (complete or partial analysis) must be accepted as of great value in clinical medicine today. No group of specialists are more keenly aware of this than gastroenterologists themselves.

Philosophically, however this study of the emotions and their bodily reactions do not do more than show that the psyche is not unrelated to the soma. There is of course no reason to suppose that this relationship is very deep. For example to ask the question, "what relation exists between the structural pattern of the body and the cognition of consciousness?" is to receive no adequate answer. When the era of mechanism passed, we soon tired of vitalism and tossed the problem of tissue function back to the sound basis of biochemistry. When the problem of tissue dynamism became too burdensome, we again passed the whole question over to the geneticist but he is a busy man and has not yet found time to theorize. This last treatment of a philosophical puzzle namely the placing of responsibility upon germ cells had the advantage of postponing any sweeping psychosomatic generalization. It brought the question down to what is contained in two primitive cells, rather than what is contained in a system-complex of tissues yet it threw no added light on the chief problem—the relationship if any between mind and matter.

The powers of the chromozones in the sperm and egg, in virtue of their contained genes, seemed limited only by the barriers set by inheritance and variation.

What relationship exists between the consciousness of the phenotype and the intricate potentialities of the genotype? Has the gene any intelligence? If not, when does intelligence appear? Psychoanalysis plainly shows that even before ratiocination is possible there exist deep biological urges in the psyche of the infant. Analysis has brought out many facts of the thought-life which normal consciousness was unaware of. Then why not assume that consciousness is a practically bottomless abyss? If such an assumption were logical then we might suppose that deep—very deep,—in the psyche there reposed tissue intelligence, physiological acumen and indeed everything needed for a complete acceptance of monism. The trouble with all this is simply that there is no evidence at all for the assumption of such a depth of consciousness. The analysts fight the postulation of the "unconscious" with all their energy, and their position is easy to understand. It is because, in the past we have attained our most useful knowledge not by assumption, but by working patiently from what we know in the direction of the unknown.

The present position is that we may *try* to think of man as a psychophysical entity if we wish, but the effort is only moderately successful. In the emotional sphere where the connection is plainest we will do well to use carefully all that psychosomatic medicine can really prove to be of value. Monism probably will not be proved by medical science. Our entire academic background is based on the evident pluralism which characterizes both the body and the mind of man.

Book Review

The Microscope and Its Use. By Frank J. Munoz and Harry A. Charipper. 334 pages, \$2.50. Chemical Publishing Co., Inc., Brooklyn, N. Y.

Dr. Munoz is a technical consultant in optical instruments and Dr. Charipper is Professor of Biology at New York University. Their collective efforts have resulted in a simple authoritative volume which fills a definite need. As stated in the preface, the intention of the authors was to write in non-technical language a small practical guide to the use of the microscope one which would be useful to the beginner and the technician and devoid of discussions of 'optics'. The intention was fulfilled admirably. The ten chapters, together with tables and diagrams, cover the subject in a very readable style. A glossary of technical terms and a selected bibliography complete the volume. It should prove useful to technicians in hospitals and research laboratories and to students in biology and medicine.

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CLINICAL MEDICINE

STOMACH

MEINERTZ, I. *Gastritis, Uleer, Carcinoma. Deutsch med. Wochenschr.* 1 of 68, p. 292, 1942

Relations between gastritis, gastric ulcers and gastric carcinoma are discussed. A common underlying etiology exists in disturbance of function, i. e., gastritis is not an isolated pathologic condition. Theories of ulcer formation are noted with emphasis on the neurogenic theory and psychic influences. Differences between gastric and duodenal ulcers are noted and the rarity of malignant changes in the latter is discussed. Therapy of ulcers is reviewed with emphasis on the need for thorough study with large series of patients, to reduce psychic factors. The ineffectiveness of l-aspartic acid (histidine) is noted in a controlled series of one hundred patients.—G. A. L.

GILL, A. M. *Evaluation of Gastrosocopy. In Analysis of 1000 Examinations. Lancet* 1 of 244 p. 533, 1943

The value of gastrosocopy in diagnosis is discussed and comparison with roentgenographic findings is made. Multiple gastric erosions can be demonstrated more clearly than by x-ray and acute gastritis differentiated from chronic. Mucosal atrophy, unexplained achlorhydria, gastric hemorrhage of unknown etiology and benign gastric tumors are some conditions which can be diagnosed with any degree of certainty only by use of the gastroscope.—I. M. Theon

PEARL, E. I. AND BRUNN, H. *Multiple Gastric Polyposis. Supplementary Report of 41 Cases Including 3 New Personal Cases. Surg. Gyn. Obs.* 1 of 76 p. 257, March 1943

The authors collected from the literature since 1926 forty-one cases of gastric polyps and include three cases of their own. Multiple gastric polyposis are either neoplastic or inflammatory in type. In the neoplastic type the muscularis mucosa and the submucosa are involved, while in the inflammatory or hyperplastic type the submucosa is not involved. Diagnosis is difficult. Epigastric pain, tenderness and hematemesis are common symptoms. Polyps near the pylorus may result in obstruction. Both the roentgenogram and the gastroscope should be used to establish diagnosis. Free acid in the fasting gastric contents is nearly always absent. 404

Radical surgery of the malignant area is the procedure yielding best results.—G. Klemm

HERRANDEZ MORALES, F. *Gastrosocopic and rectosigmoidoscopic observations in schistosomiasis mansoni. Preliminary report. Puerto Rico J. Publ. Health Trop. Med.* Sept. 1942 1 of 18

This is the first instance in the literature of a report of the gastrosocopic findings in patients with Schistosomiasis. The paper includes the results of such examinations made on 10 cases together with a table showing the distribution as to race, age, sex and amount of free HCl following histamine stimulation.

The results may be summarized as follows: Gastrosocopic findings—

1. Atrophic gastritis was found in 1/3 of the patients 2 of which also had sprue. Hypoacidity in 1 normal in the others.

2. Hypertrophic gastritis in 3 associated with gastrointestinal disturbances for a period of years.

3. Acute superficial gastritis with atrophy in 1.

4. Atrophy and hypertrophy combined in 1 case. Rectosigmoidoscopic findings showed (7 patients):

1. Atrophy in 2 patients, who also had gastric atrophy associated with sprue.

2. Atrophy with inflammation in 2.

3. Acute superficial inflammation in 2.

No definite conclusions may be reached from this report. Perhaps, the authors suggest a sequence of the findings may obtain in large series of observations on Schistosomiasis.—Jose L. Garcia Oller

BOWEL

SYMES, S. AND AMBRUSKO, I. *The Microscopic Diagnosis of Radiopaque Substance in the Vermiform Appendix. Surgery* 1 of 13, p. 561, April, 1943

The authors present a series of cases in which they found radiopaque substance in the lumen of appendices. Because of the implications it carries for the pathologist, roentgenologist, and surgeon they report the microscopic appearance. A total of 1,395 appendices were examined and radiopaque substance, apparently barium sulfate, was found in seventeen. This observation was verified by a history of either a preoperative gastrointestinal series or a barium enema in all seven.

teen. The substance (accepted as being barium sulfate) varied in amount and was distributed free in the lumen, or else was mixed with feces, or incorporated in fecaliths. When in great amounts it appeared as a white, opaque substance in the gross specimen as well as in embedded segments and in mounted sections. Under illumination of microscopic sections the substance was observed as glistening, green-gray and refractile. It appeared more or less as an amorphous material, being darker with subdued central illumination. It also appeared as a glistening substance under dark field examination and in the polarizing microscope presented no crystalline structure. Commenting upon the recognition of barium sulfate in the lumina of appendices, the authors suggest that this may be used as a method to check the frequency with which barium sulfate enters the lumen of the appendix without detection by the roentgenologist. The questions are also raised as to whether or not this may be a direct histopathologic sign indicative of disturbance in evacuation of the appendix and as to whether or not this sign can be correlated with the clinical and radiographic picture of "chronic appendicitis"—R. J. Revelin

JORGE, J. M., FELDMAN, L., AND ITURRIOZ, T. *Inguinoscrotal Hernia Containing the Stomach. Semana Medica*, Vol 50, p 301, Feb., 1943

Within a large inguinoscrotal hernia of the right side there was found (by roentgenogram and confirmed by autopsy) a portion of the stomach and segments of intestine in a man aged 66. Published reports of 22 other such hernias were found. The authors state that the condition does not necessarily interfere with the patient's health—G. Klenner

SCHOEN, H. *Appendostase? Deutsch med Wochenschr*, Vol 68, p 222, 1942

Atony of the appendix was noted in a 34 year old female. Contrast media remained in the appendix for one month and pituitary extracts did not cause emptying. The condition is explained through destruction of the innervation in a previous attack of typhus—Courtesy Biological Abstracts

JACKMAN, R. J. *Anal Abscess and Anal Fistula in Association with Regional Ileitis. Report of Case. Proc Staff Meet Mayo Clinic*, Vol 18, p 154, May, 1943

There is a tendency for fistulas to form in association with regional ileitis. Originating in the involved ileum, the fistula may end in the abdominal wall or some viscus. Jackman calls attention to the frequency of this association. From the records of 114 cases of regional ileitis, Jackman found 31.6 per cent of them to have had anal abscesses or fistulas. Indeed, 70 per cent of the patients entered the Mayo Clinic primarily because of anal fistula. The author concludes "The combination of anal abscess or fistula, plus any vague intestinal disturbance in a young adult should make the clinician suspect the possibility of regional ileitis"—F. X. Chockley

BRADLEY, W. H. *Epidemic Nausea and Vomiting. Brit Med J*, p 309, March 13, 1943

An epidemic of nausea and vomiting occurred in a community in England mainly among school children but also among the general population. For recognition of the true character of the disease, food poisoning and dysentery must be ruled out. The epidemic of nausea and vomiting reported by Bradley is believed to have been due to an upper respiratory infection, probably of virus origin, which had an incubation period of two days to one week. The disease was communicable and the passage of entry was the upper respiratory tract. Vomiting was often projectile. Nausea without vomiting was common but was then associated with dizziness and fainting spells. Temperature was only slightly elevated. The abdomen was negative—G. Klenner

HALEY, J. C. AND PEDEN, J. K. *Suspensory Muscle of the Duodenum. Am J Surgery*, Vol 546, p 59, 1943

This study is based on 77 cadavers. Careful examination led to the conclusion that the suspensory ligament or muscle of the duodenum originates from the right crus of the diaphragm and the fibrous tissue about the coeliac artery. It is inserted into the duodenum after coming down behind the pancreas and in front of the left renal artery. The point of insertion was not found to be constant, in 61 per cent of the cadavers this was in the third and fourth parts of the duodenum. In 18 per cent of the cadavers the ligament and muscle were absent. The possibility that the fibers of the suspensory ligament may be the cause of partial obstruction when the attachment is solely to the duodenojejunal flexure is considered, but is not believed to be great—I. M. Theone

ACKERMANN, W. *Diverticula and Variations of the Duodenum. Ann Surg*, Vol 117, p 403, 1943

Examination of 50 cadavers revealed that 22 per cent had diverticulae of the duodenum. No diverticula were found in the first portion of the duodenum, 5 were found in the second portion, 5 in the third, 1 between the second and third, and 3 in the fourth portion. Eight of the eleven cadavers had single diverticula and the remaining three had double diverticulae. All developed from the pancreatic border of the duodenum and most were in the substance of the pancreas. This study thus revealed that duodenal diverticula are more common than believed from data obtained by x-ray examination. Incidental to the subject proper, is the notation that the papilla of Vater is not constant in location and that the duodenum varies greatly in length and shape—I. M. Theone

LIVER AND GALL BLADDER

WALKER, WILLIAM J. *Pathogenesis of Cholelithiasis. J Amer Inst Homoeopathy*, Vol 36, p 13, 1943

Theories of formation of gallstones are reviewed. The three important etiologic factors are infection, bile stasis and faulty cholesterol metabolism—Courtesy Biological Abstracts

STLINER, PAUL L. *The Incidence of a Carcinogenic Factor in the Livers of Cancer, Anomalous, Cirrhotic and Negro Patients (Cancer Research, Vol 3 p 385 Jan, 1943)*

Subcutaneous injections of human liver extracts in mice demonstrated the presence of a carcinogenic factor in the livers of cancerous and noncancerous patients. The induction time was 6 months. Of the tested extracts, 21 per cent were active. The activity was not related to any special site or type of tumor but it seemed to be especially prevalent in tumors of the endocrine system. There was no special relationship to any type of major disease, tumor or nontumor. There was no difference in age groups, in the two sexes, in whites and Negroes, or in cirrhotic as compared with noncirrhotic livers. The carcinogenic factor does not increase with age. Experimental factors such as number of injections or stock of mice, didn't influence the number of induced sarcomas. Possibly the type of solvent may influence results, all induced sarcomas having occurred when sesame oil was used and none being elicited in experiments with triethylol. However, an insufficient series was run with the latter to be conclusive. Since only 12 per cent of livers were active, probably the carcinogenic factor is not formed from a normal constituent of the liver.—Ivan F. Bennett.

CORTI, M. B. *Diagnosis of Pseudo obstructions of the Bile Duct. Anais Paulistas Med e Cir Vol 44, p 190 1942*

A discussion of the possible causes of apparent obstruction of the bile duct and resultant jaundice, together with suggested methods of determining the true conditions. Interpretations are based on case history studies.—Courtesy Biological Abstracts.

ROCH, M. AND FEHR, J. J. *Cirrhosis in the Geneva Medical Clinic During 1931 to 1940. Rev. Med Suisse Rom, Vol 62, p 81 1942*

During the period 1931-40 230 cases of cirrhosis of the liver were observed. The diagnosis was checked by autopsy in 118 cases. Although there were 35 times as many male as female alcoholics 31 per cent of the patients with cirrhosis were women. This suggests that the hepatic glands of the female are less resistant than are those of the male. Etiologically, alcoholism ranks first in the development of cirrhosis.

It was always present in the cases diagnosed as Laennec's cirrhosis (79% of the total) and often present in other types. Many years of drinking are necessary to produce cirrhosis. In one case the drinking of beer alone was responsible for the development of cirrhosis. Usually wine is the cause alone or in association with the drinking of aperitifs. Digestive disturbances appeared in the majority of cases after the development of cirrhosis. They must therefore be considered as secondary and cannot be the cause of the condition. Neither syphilis nor tuberculosis seems

to have any etiologic significance in the production of cirrhosis.—Courtesy Biological Abstracts.

ALLEN, J. G. AND JULIAN, O. C. *Arch Surg, 45, p, 691, 1942*

Sixty one patients with prothrombin deficiencies were studied. In group one (28 patients), consisting of cases with obstructive jaundice, oesophageal carcinoma, external biliary fistula, and gastric ulcer, the exclusion of bile salts from the intestine was responsible for the low vitamin K absorption. Treatment which insured good absorption resulted in immediate elevation of the prothrombin level. Group 2 (31 patients), consisting of cases with jaundice of intra hepatic origin, were very little relieved by treatment. The prothrombin level remained low. Group 3 patients had cirrhosis of the liver and ascites but did not have jaundice. Continued vitamin K therapy raised the prothrombin level in two cases but failed in another two cases. The authors do not believe that the degree of prothrombin deficiency is indicative of the extent of liver damage and consequently conclude that prothrombin levels are not accurate indices of liver function.—G. Klemm.

ULCER

BEIGBLICK, W. *Insulin shock therapy in ulcer. Deutsch med Wochenschr 68, p 17, 1942*

The mechanism of action of hypoglycemic therapy in peptic ulcer is discussed. Insulin hypoglycemia causes hyperemia of the gastrointestinal tract, an increase in gastric secretion and bile, and peristalsis. Insulin also causes an outpouring of Na in the gastric juice with retention of K, while histamine has the opposite effect. Insulin corrects the acidotic tendency of ulcer patients. The role of the autonomic system in insulin hypoglycemia is mentioned and its effect on cholinesterase and acetylcholine content of organs is being studied. Adrenal hypertrophy following repeated insulin treatments may play a part in favoring healing of ulcers, especially those caused by allergies. Courtesy Biologic Abstracts.

SURGERY

BURGOIS, B. G. *The surgical treatment of gastroduodenal ulcer. L'Union Medicale du Canada, v 72 p 267, March 1943*

This is a review of the late chief surgeon of the Notre Dame Hospital in Montreal which was presented in a symposium before the 17th Congress of French-speaking doctors of North America. Several of the more usual surgical procedures are discussed. Consideration is given to the most frequent complications of chronic ulcer—obstruction, perforation and hemorrhage. Immediate operation is necessary in perforation but surgery is not favored in hemorrhage.—M. H. F. Friedman.

The Treatment of Amebic Dysentery

By

HORACE W. SOPER, M.D. F.A.C.P.
SAINT LOUIS, MISSOURI

THE *Endamoeba histolytica* was discovered by Loeb in 1875. Later investigators proved that the organism was the cause of a distinctive type of dysentery. It has three stages in its life cycle:

1. The trophozoites, the living motile organism
2. Precystic stage
3. Cystic stage

It lives in the small intestine and colon and has tissue invasive power. It frequently affects the liver, and is found more rarely in other organs. The diagnosis is usually made by microscopic examination of the feces. Warm the feces to 100°F, search for small clumps of mucus and examine the fresh specimen. It may be stained and cultured, or Craig's* complete fixation test may be employed.

The protoscope and the cotton swab applicator have given me the best results in diagnosis, frequently demonstrating the organism when skilled laboratory technicians have failed to find it in the feces specimen.

Impure water supply is the chief agent for transmission of the disease. The cysts may live for several days in moist fecal matter. Flies may contaminate food and many epidemics have occurred. Many persons who have survived the acute stage still retain the infectious agent in ulcers and are known as "carriers."

Treatment—Craig and Faust (2) advise the employment of emetine hydrochloride, gr. 1, subcutaneously daily for a period of twelve days followed by a course of chiniofon, vioform or carbarsone. They warn against the employment of emetine intravenously, as they have encountered two fatalities from its use. P. W. Brown (3) and Bergen (4) of the Mayo Clinic also administer the drug subcutaneously.

Twenty years ago I began to employ emetine** intravenously in the treatment of amebic dysentery. I saw many early cases, in patients returning from a visit to the South. I made daily proctosigmoidoscopic examination and demonstrated the acute early lesions. They are from one-tenth to one centimeter in diameter, grayish-white in color, somewhat raised above the mucosa. When wiped off with a cotton applicator, they leave a surface which oozes blood. The material removed reveals swarms of *Amoeba histolytica*. This picture of the acute stage is very characteristic. Jerome Lynch said, "It looks like smallpox lesions of the skin."

I observed that the lesions disappeared by the third or fourth injection of emetine. Seven consecutive daily doses were given, followed by a seven-day course of

stovarsol (acetarsone) one 0.25 gm. tablet three times daily before meals.

No toxic symptoms were observed after the emetine injections. It was always given slowly (with the patient lying down). Some patients experience a feeling of evanescent giddiness and fulness in the head after the initial dose.

I had in former years given the emetine treatment to advanced cases with deep ulcerations (carriers) over a period of three to four weeks' time and had produced toxic symptoms—multiple neuritis, myocardial involvement, etc.—therefore, was aware of its toxicity when administered over too long a period of time. This experience convinced me that the failure of the emetine to cure the chronic carrier was due to the fact that the induration surrounding the ulcer acted as a barrier. I firmly believe that emetine is highly specific in its action in patients not in the carrier stage, when given intravenously. It reaches the whole circulatory area in more concentrated form than when given subcutaneously.

In a series of 302 cases, I had but one recurrence, viz., in a large boy, aged 14 years, who had received but one-half grain dosage of emetine. My impression was that the treatment outlined above was applicable only to the early cases, but since the Chicago epidemic I have employed the treatment in cases in which the infection has existed from one to two years. These patients were not chronic carriers with deep ulcerations, they had a milder type of the disease with indefinite symptoms.

Craig in a personal communication informs me that the two fatal cases occurred in soldiers in 1916. Cardiac failure occurred but he does not know the size of the dosage or the length of time of administration. The warning issued against the employment of emetine intravenously by this eminent authority has probably deprived thousands of patients of the benefit to be secured by this method. It is far superior to the subcutaneous route, and in the end requires less quantity of the drug. I wish to go on record as emphasizing that emetine given as I have employed it is not toxic to the patient but is extremely toxic to the *Amoeba histolytica*.

The Complications of Amebic Dysentery—Abscess of the liver occurs often in late neglected cases. The diagnosis is made from the history of a dysenteric attack, the temperature curve and the finding of enlargement or tender areas in the liver upon palpation.

Hepatic Abscess—The treatment of amebic abscess has recently been presented by Joslyn (5). He points out the high mortality rate which follows surgery, and emphasizes the tremendous value of the aspiration.

* I have always employed Burroughs-Wellcome Company ampules.

** The reader is referred to Craig and Faust's book for full details.

method of treatment is suggested by Rogers (6), Ludlow (7) and Thurston (8).

In this connection, I may be pardoned for relating a personal experience. While an interne in the St. Louis City Hospital in 1894 (where Joslyn was interne in 1935) I had charge of the tuberculosis ward. Dr. Greenfield Sluder, acting superintendent, advised me to try to prove that some of the inmates of the ward did not have tuberculosis. The result of the investigation was four cases of amebic abscess of the liver. Three of the patients were operated upon and all died. The abscess was aspirated in the fourth patient and 500 c.c. of characteristic pus was evacuated. Acting upon my advice he refused surgical operation and made a rapid and permanent recovery. It was of interest to note that the temperature curve was atypical, being higher in the morning than in the evening in contradistinction to the curve characteristic of tuberculosis.

Abscess of the lung occurs rather often in late cases. Abscesses in the brain, skin, lymph glands and bladder have been reported.

The late ulcerative lesions in the colon are very intractable to treatment. Ulcers with ragged undermined edges, the floor covered by necrosed material containing the active ameba may be seen at times with the proctoscope. Craig has emphasized that the ulcers are frequently connected by sinuses beneath a

still intact mucous membrane. He advises chinoson as the drug of choice in the treatment of carriers. It is given in 0.25 gm. tablets three to four times daily (adult dosage) for a period of eight to ten days. The full dose sometimes causes a severe diarrhea and it should be started with a small daily dose, gradually increasing it. The course may be repeated after an interval of two weeks time has elapsed.

Late chronic destructive colonic lesions may respond to surgical treatment as recently emphasized by Bassler (9).

I have observed many cases of amoebic dysentery that were treated elsewhere by the subcutaneous injection of emetine, while some were cured they had received much more of the drug than that given by my seven consecutive days by the intravenous route.

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The Treatment of Peptic Ulcer

By

HORACE W. SOPER, M.D., F.A.C.P.
SAINT LOUIS, MISSOURI

THE whole subject of the treatment of peptic ulcer requires revision corresponding to our knowledge of infection in the etiology, caloric and vitamin values in foods. In the literature the Sippy method is usually mentioned when surgical procedure is not advised. The Sippy treatment, frequent milk feedings and administration of large dosage of alkalis, results too often in alkalosis, malnutrition and infection with malta or undulant fever, notable in the great loss to the nation of the late Edsel Ford. It is estimated that over 10,000 cases of undulant fever occur in this country annually.

Simple Uncomplicated Ulcer. The patient (ambulant of course) is given two hour feedings of evaporated milk* and raw eggs in emulsion form with Ralston wheat germ breakfast food, custards and strained cream vegetable soups all made from the evaporated milk, Jello, and one tablespoonful of honey to one glass of orange juice. All the essential vitamins are present in the above list, but I fortify the B complex by giving three No. 00 gelatine capsules daily filled with brew-

ers' yeast**. After about four weeks three meals daily are given including scraped beef, minced chicken, scrambled eggs, Gerbers' canned vegetables, Libby's homogenized strained vegetables and fruits, milk toast, plain toast with micon and jellies, ice cream and light cake and similar light desserts, avoiding roughage, high seasoning pastries and above all raw or pasteurized milk, insisting on evaporated milk only. This regimen is finally augmented by the addition of meats, cooked vegetables and fruits, etc., until a general rational post ulcer diet list is achieved, avoiding raw salads and raw and pasteurized milk.

The above method of treatment is not advisable for the ulcer patient aged fifty or more because of its high cholesterol content; therefore we must omit egg yolk, internal organs, fat meats, etc. from the dietary. Constipation usually results from such a smooth diet and I employ a mixture of light and heavy calcined magnesium, equal parts, to be taken in the morning upon arising, a heaping teaspoonful more or less to regulate elimination.

The feces of all ulcer patients should be examined frequently for occult blood reaction. If the reaction

* I advise the Pet brand.

** I employ the Squibbs' malted yeast powder which also contains niacin, pantothenic acid and biotin.

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is constant, malignancy is suspected and surgical exploration is advisable, particularly if the lesion is located on the greater curvature of the stomach

The small pin point perforating ulcer is treated by bed rest, small frequent feedings of gelatine water and egg albumin water, and daily intravenous injections of 2000 cc of 10% glucose in normal saline solution. In about one week the evaporated milk and egg emulsion may be employed

The large perforating ulcer with early signs of local peritonitis demands immediate surgical operation. The jejunal ulcer following gastro-enterectomy is usually considered as a surgical problem, however I have records of twelve patients in whom the ulcer was healed by the following method. The Levin duodenal catheter is passed intranasally slowly with the patient lying on the right side sipping gelatine water. The X-ray demonstrates that it passes through the pylorus. Jejunal feeding is given using the evaporated milk egg emulsion, honey and orange juice containing the yeast powder in suspension (about three heaping teaspoonfuls of the yeast daily). The patient is kept in bed for two weeks, after which time he is permitted to sit up. The tube can be kept clean by dropping lanoline in the nostril and swabbing the tongue and mouth with a 2% solution of mercurochrome. The patient is allowed to drink gelatine water i. e. the gelatine is allowed to "jel" and a heaping tablespoonful of it is stirred up in a glass of cool water.

HEMATEMESIS

Gastric and duodenal ulcer is the cause of hemorrhage in about 75 per cent of the cases. Since the presentation of my paper on the treatment of hematemesis by the retention catheter in 1931, we have had considerable experience and increasing confidence in the rationale of this method of treatment. It was really an evolutionary process growing out of the Levin gastro-duodenal catheter in postoperative conditions. We learned that the Levin tube did not excite gastric contraction and peristalsis, that it did not incite secretion and could be readily introduced by the nasal route in the unconscious patient. The absence of a metal "Bucket" on the tip of the tube is of great importance, as this foreign body might induce contraction or peristaltic movements. The Levin tube is formed like the ordinary urethral catheter and has no such objection; therefore, I was emboldened to employ it in the treatment of gastric hemorrhage. I had always hesitated to use the ordinary stomach tube following a large hemorrhage because of the excitement, struggles and eructations of the patient incident to its introduction. This method of gastric lavage was employed by Ewald, (2) Kaufman, (3) Hurst (4) and others. Kaufman very clearly described the advantages of lavage as follows: "These stagnating masses are usually very sour and fermenting, and their presence not only causes nausea and pain but acts very harmfully by constantly irritating the mucous membrane to intense hypersecretion, thereby further increasing the amount of gastric contents. The removal of the fermenting masses not

only relieves annoying symptoms of gastric irritation but eventually brings about a direct cessation of the bleeding by allowing the emptied stomach to contract and thus aid in the occlusion of the eroded vessel."

The Levin soft rubber gastric catheter is passed intranasally into the stomach. The large Luer syringe is attached and normal saline solution is injected and withdrawn repeatedly until the stomach is clean. It is remarkable how easily a large blood clot that fills the entire stomach is broken up by this method. The technique of passing the tube is of extreme importance. The nasal mucosa should be shrunk with a 2 per cent solution of cocaine hydrochloride. The tube should be passed slowly down the esophagus and the patient allowed to drink a swallow of water with each advance of the tube. If passed quickly, it may coil and form a troublesome knot. The syringe should be used often and the tube kept free from small clots, a glass tube joins the nasal tube to a rubber tube which leads to a bottle on the floor. The character of the secretion passing through the glass tube should be observed frequently and tested often for acid with fresh congo red paper. Liquid petrolatum is dropped into the nostril three times daily, and if the patient complains of sore throat, swab with 2% mercurochrome solution. The use of a local hemostatic is of extreme importance. I employ thromboplastic solution,* injecting it undiluted directly into the stomach after the blood clots have been removed or, in cases of hepatic cirrhosis, into the lower esophagus. The fine small black clots that result are characteristic of this hemostatic. The tube can be easily introduced in the unconscious patient.

Sippy's treatment was not merely the administration of large doses of alkalis and milk diet but it consisted in frequent gastric lavage. His dream was to keep the stomach free from acid secretion. This is very readily accomplished by gastric siphonage. One of the objections raised by gastroenterologists has been that by siphonage we withdraw chlorides and other essential elements from the system. The answer is that we are replacing them by means of glucose in normal saline solution intravenously as well as per rectum. Two thousand cc of the ten per cent solution means 800 calories introduced daily. I am an advocate of large blood transfusions in massive hemorrhage. The fear of raising blood pressure and blowing out a fibrous clot is a myth.

We now rarely pass the tube down into the duodenum but continue to leave it in the stomach giving fresh egg albumin water and gelatin water freely by mouth and allowing what may siphon out to do so. The major portion of the mixture will pass down out through the pylorus. By the third day we begin to feed a high calorie mixture consisting of an emulsion of raw eggs and evaporated milk. The patient is permitted to drink the mixture, feeding every two hours. A weak solution of sodium bicarbonate may be introduced from time to time to correct any acid discomfort, which, however, rarely occurs. Congo red paper is employed to determine the degree of acidity at the

* Ampoules of fibrinogen

end of the gastric tube. A hypodermic injection of ascorbic acid ampoule once daily as advised by Rivers and Carlson (5) of the Mayo Clinic, yeast is also added to the egg and evaporated milk emulsion, gradually adding other soft foods. The tube is usually removed at the end of two weeks.

The above method of treatment permits early diagnosis of arterial bleeding. As a rule, small clumps of dark bloody mucous appear in the glass connecting tube. If twenty-four hours or more after the initial livage bright red blood is observed, it means a "spurter" and immediate surgery is advised. Our records reveal twelve patients have been saved by operation which disclosed the bleeding vessel. Under the old expectant method, the diagnosis of arterial hemorrhage cannot be made until too late to save the patient by operative procedure. Vomiting of large masses of clotted stagnated blood often occurs the second or third day, and the physician does not know whether it is a secondary hemorrhage or just the initial mass that has remained in the stomach.

In consultations, the chief error that I have observed is the failure to completely empty the stomach in the livage which should be done with a 250 c.c. Luer syringe, using force and being sure that the stomach is entirely emptied, repeatedly filling the syringe and withdrawing as much as possible until the solution returns clear. The Meulengracht method of feeding at once a large mixed diet of meat, strained vegetables, etc., cannot be condemned too severely. It is unscientific, and does not consider the underlying pathology of ulcer.

Duodenal ulcer occurs quite frequently in patients afflicted with *polycythemia vera*. One of my patients, male, aged thirty-eight, was seen in 1915. He had duodenal ulcer which recurred frequently. He also had *polycythemia vera*. Finally, in 1928, he was given small daily doses of phenylhydrazine which reduced his red cells to normal. The dosage required to maintain this condition varied from one-sixth to one-half grain. The ulcer healed promptly and he has had no recurrences for a period of ten years. I have records of twenty-four cases who presented the combination of duodenal ulcer and *polycythemia vera* all of whom have responded well to the daily small dose of phenylhydrazine.

Cardia lambia infestation frequently produces superficial ulceration in the duodenum. Treatment was very unsatisfactory inasmuch as the parasite was difficult or impossible to eradicate. I found that Atabrine as recommended by Galli-Valerio (6) and later by Teron (7) was a specific requiring 0.1 gm. of the

drug three times daily for five days. In my series of twenty cases, no recurrence of ulceration appeared after this treatment.

Among the new methods of treatment, I mention vaccines, nonspecific proteins, metaphen, mucin synodal, larostidin and bismuth. In my opinion they are all to be rejected. *The character and quality of the daily ingested food spells success or failure in the healing of ulcer.*

Gastric siphonage initiates rapid and complete healing of peptic ulcer, as I have demonstrated in a large number of cases. The physician is always in control of the situation with exact knowledge of intragastric conditions. It is a "direct attack" at the site of the lesion instead of the usual watchful, waiting, expectant plan of treatment.

Lusterman (8) emphasized the necessity of treatment or control of the neurosis so often associated with ulcer. I have found a capsule containing gr 1/500 of atropine and one grain of Veronal given every four hours to be extremely efficacious in patients of this class.

The ulcers with recurrent bleeding attacks should receive surgical treatment. They are usually located near the pylorus, either in the duodenum or stomach and are non-obstructive. The operation of choice should be subtotal gastric resection. In my experience, gastroenterostomy in such cases has always been disastrous. *The pyloric obstructive ulcer* with the development of scar tissue always responds well to gastroenterostomy. Surgeons sometimes exclaim, "Three weeks after operation and he now eats everything!" But the post operative period should always receive the careful regimen as outlined above for simple uncomplicated ulcer.

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Peptic Ulcer at Fort Sill

By

ROBERT C. KIRK, CAPTAIN, MC, AUS

FORT SILL, OKLA

PEPTIC ulcer plays the leading role in digestive diseases in the military service. It leads all other gastro-intestinal conditions as a cause for discharge from the army. It is in general similar to that encountered in civilian life. The incidence rate has increased considerably in both areas in the past three or four years. However, it must be recognized that in the previous World War, 1914-18, precise diagnosis of gastro-intestinal disease was in its infancy and our knowledge of the effects of military service on peptic ulcer must be gained from studies made during and after our present conflict. It is for this purpose that a survey has been made of peptic ulcer at Fort Sill.

The present study was made during the period October 1, 1942 to March 1, 1943. During this 5 months period 385 patients were admitted to the gastro-intestinal section for study; those patients were all privates or non-commissioned officers at this post. Since there is a large reception center and a replacement training center here, as well as many smaller technical units which are sent here for training, it is felt that these admissions represent a very integral cross-section of our present training army. It is probably well understood that a station hospital cares for practically every soldier marked unfit for duty, but this does not necessarily mean that the disease process is acute. Of these 385 men, 50, or 12.9%, were found clinically, with X-ray confirmation, to have peptic ulcer.

Only one case of gastric ulcer was seen, and for statistical purposes the 50 cases of duodenal ulcer will be treated as a whole. It should be said that the ratio of duodenal ulcer to peptic ulcer of 50:1 is higher than any previously reported series. No satisfactory explanation for this occurs to us.

MATERIAL

Of the 50 soldiers in this series, 38 were white and 12 were negroes. The ages were between 19 and 41 as would be expected, but when inquiry was made into the duration of symptoms, there was a noticeable "shift to the left." Three men dated their onset of symptoms to the first decade (seven years, seven years, and eight years), ten to the second decade, 24 to the third, and only 13 to the fourth. The oldest man at the onset of his symptoms was only 36. Thus it appears to be a disease of young men, which satisfactorily accounts for its high ratio in the army. These cases were further divided into acute and chronic by the arbitrary method of calling all cases with less than 12 months of symptoms acute. By this method 36 men were called chronic ulcer with an average duration of symptoms of 5.5 years. There were 14 so-called acute cases with an

average duration of 6.5 months. Of these acute cases 11 were in line of duty, in other words, had no symptoms prior to coming into the service and symptoms first developed after sufficient service to be considered a result of it. Only three men developed acute symptoms within the 12 months prior to induction, of which more later.

SYMPTOMATOLOGY

That pain is the outstanding characteristic of peptic ulcer is a fundamental known to all. Its chronicity, periodicity, quality, and relationship to food taking, is classical. However, this is not enough to strongly eliminate other possibilities, particularly, that rather vague clinical diagnosis of "gastritis." Careful questioning in this series has brought out the rather surprising fact that 96% of these men have been awakened from sleep usually around 2 to 3 a. m. by a pain described as burning by 78%, and/or boring by 70%, which in 52% was accompanied by pain in the back, usually described as an ache. This painful triad has been pathognomonic of duodenal ulcer. Not mentioned in one important textbook but occurring in 88% of this series was intolerance to greasy foods. No other food or combination of foods equalled these as an admitted cause of gastric distress. Considerable vomiting, frequently severe, occurred in 78%. Lastly, and possibly peculiar to the army were the complaints of restlessness in 92%, sleeplessness in 78%, easy fatigability in 76%, and nervousness in 74%. Constipation listed as a common complaint in one text, occurred in less than 20%. Palpitation of the heart was complained of more than twice as frequently.

PHYSICAL FINDINGS

Soreness in the mid-epigastrium was present in 47 out of the 50 cases. "Yon Cassius has a lean and hungry look," frequently quoted as proof that he had an ulcer, has had a counterpart in only 28% of these men. Depression noted in the facial expression, when present, was marked but occurred in only 26%. Weight loss was seldom extreme, averaged 10 pounds, and its occurrence was confined almost exclusively to those in whom vomiting was an outstanding symptom.

LABORATORY EXAMINATIONS

Here the X-ray is of prime importance as a "positive" report must be made to establish the diagnosis. Repeat examinations were frequently made and all doubtful cases have been excluded. A definite deformity with either evidence of obstruction or penetration was present in 12. X-rays were not taken on the three remaining cases who had perforations and surgical repair.

The white blood counts taken upon admission to the hospital varied from 3 400 to 13 200 and the differential count was in no case unusual. The sedimentation rate varied from 15 mm per hour to 15 mm per hour, with an average of 6.5 mm. 0 to 10 mm is considered normal.

Gastric analysis was performed in most instances, using the Ewald meal, although the alcohol meal was also used on a few of the earlier cases. The findings in each case were totalled and the average free fasting acid was 23.3° going to 35° after test meal. The total fasting acid was 46.8° and rose to 54.4° after test meal. Occult blood was present in the fasting contents of 14 individuals.

TREATMENT

Since in the army, diagnosis receives a high priority because of the necessity of early disposition, regular ulcer management was withheld in doubtful cases until a gastro-intestinal series was completed. It had been our experience that bed rest and a milk and cream diet with the usual anti-spasmodics and anti-acids would in some instances give such immediate relief that a following gastro-intestinal X-ray study was occasionally or even frequently negative. This would be well if soldiers were available for follow-up. However, soldiers coming from organizations departing for foreign service are subjected frequently to the many factors considered favorable for recurrence of peptic ulcer. It was decided that more certain diagnosis could be afforded by having the X-ray made during the time of acuteness of symptoms. So well has this worked that in this reported series there was only one case with normal gastro-intestinal X-rays whom we considered probably had a duodenal ulcer clinically. On the positive side there were several in whom the diagnosis was considered doubtful on admission to the wards because of repeated negative G.I. series at other civilian and army hospitals, who, nevertheless, had a positive X-ray diagnosis of duodenal ulcer following this procedure.

COMPLICATIONS

There were three cases of acute perforation, occurring while the men were at duty. Two of the anterior and one of the posterior wall of the first portion of the duodenum. They were operated and recovered with no complications. There were four cases of hemorrhage moderately severe in each. All four were placed on hourly feedings for the first 48 hours in a sort of modified Meulengracht manner. There were no further hospital complications arising in any of this group, nor in any of the uncomplicated cases.

DISCUSSION

In spite of the many uncertainties inherent in a discussion of peptic ulcer, there is a continuing interest in the disease. Jones (3) in his review for 1941-1942 discusses 40 articles pertinent to peptic ulcer, and the Journal of the American Medical Association devotes 2 issues, (4) (5), to a symposium on the subject. Statistically our series is too small to attach a great deal of significance to the percentages reported. Flood, (16) in his report of a comparable series of 75 soldiers with

ulcer had a ratio of 18 duodenal to 1 gastric ulcer. Nevertheless, 48 more cases have been seen since this initial study, with only one additional gastric ulcer demonstrated which alters the Fort Sill ratio only slightly.

That the acidity of the gastric juice is of extreme clinical importance in the management of peptic ulcer in the individual case, no one can deny. However, recent articles continue to demonstrate its complexity, (4) (5) (6) (7) (8) (9) (10). It would appear that much of our knowledge of gastric secretion must await clarification by the work in isotopes, (11). Diagnostically in the individual case there has been little correlation between the severity of symptoms and the gastric acidity. There were 10 patients in this series of 50 who produced no free fasting hydrochloric acid. There were seven more who produced less than 15° of free fasting hydrochloric acid. The average for the whole group as previously stated was 23.3°. A control group of 51 cases representing all other types of gastro-intestinal diseases and complaints had a free fasting hydrochloric acid average of 13.3°. We agree with Brown and Dolkert (12) that the gastric analysis in duodenal ulcers is of little or no diagnostic importance.

We continue to be impressed with the intolerance these patients show toward "greasy foods." Smith has very recently shown (13) that 17.7% of normal individuals exhibit undesirable objective symptoms from eating meals prepared with lard. This still leaves 70% of our group unexplained. Preliminary use of bacon grease as a test meal has not progressed to the point of reporting, but a few suggestive rises in gastric acidity following its use have been already noted.

PSYCHO-SOMATIC ASPECTS

Recent editorials (14) (15) and a review (17), combined with Wolff's work, (18) (19), have served to bring to the attention of a wide number of physicians the challenge of emotional impacts on peptic ulcer. When this study was begun superficial thinking on the part of the author resulted in the feeling that considerable light could be thrown on this problem within the army. It would seem that the prospects of becoming a soldier, followed by induction into the army with the similarity of living, food, and training facilities made ideal conditions for such a study. Actually only three men developed acute and primary onset of symptoms within the 12 months preceding induction and hospitalization. In no case could a definite relationship be established with the prospect of certain military service. Wolff's ulcer case histories showed, "prolonged emotional turmoil involving mainly conflict, anxiety, guilt, hostility and resentment." Every medical officer has seen a certain number of soldiers who have had all the above emotions with the possible exception of guilt, admittedly preceding and following induction in the army. On the gastro-intestinal service these soldiers fitting this description very closely have in almost every instance, been hospitalized for pernicious vomiting, but in no single case has a duodenal ulcer been demonstrable.

Of the 11 soldiers developing ulcer symptoms for the first time while in service, it is easy to say that failure to obtain a promotion, transfer to less desirable posts "alerting" for foreign service, constant and unremitting obedience to orders can satisfactorily establish the background of their ulcer. Actually in only a few of the psycho-neurotic personalities did these factors predominate. Outstanding was a history of onset of gastro-intestinal complaints while on maneuvers eating field rations. Even overnight field problems on field rations could be relied on to produce exacerbations. Further doubt seems cast on the emotional concept of the genesis of ulcer by the inescapable fact, at least in this hospital that patients with proven duodenal ulcer respond promptly on standard ulcer management. Complete relief of severe pain within 48 to 72 hours after being put on strict management was the rule rather than the exception. Quite the reverse occurred in the "typical psychoneurotics." No relief was admitted by the great majority when they were hospitalized for many weeks and either sent to duty or released from the military service on surgeons' Certificate of Disability for Discharge.

SUMMARY

1 50 cases of proven duodenal ulcer have been seen with only one case of gastric ulcer.

2 No correlation has been obtained between the gastric analysis and the severity of the ulcer or of the complaints.

3 Mid-epigastric pain occurring late at night and radiating into the back appears pathognomonic of duodenal ulcer.

4 Intolerance to greasy foods seems to be the greatest obstacle to satisfactory military service.

5 The incidence of peptic ulcer in psychoneurosis does not appear increased.

6 The emotional concept of the genesis of ulcer is not supported by the reported cases.

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Vitamins in Gastro-Intestinal Disease *

By

LOUIS PELNER, M. D.

BROOKLYN, NEW YORK

OPTIMAL nutrition can contribute much towards a trouble-free human life. The American dietary is considered to be remarkably inadequate. I am tempted to quote a popular commentator who advised, "How to starve to death on three meals a day." He undoubtedly meant vitamin starvation, and he surely meant American meals. That is why optimal nutrition has so much to offer us. Of course, nutrition concerns other substances besides vitamins, indeed minerals, and the protein building stones, amino acids, are fully as important.

Most stress has been placed on the deficiency of Vitamin B₁, which is undoubtedly true. But there can be no doubt that Vitamin C and D deficiencies are equally as prevalent, although more difficult to diagnose.

Added vitamin intake besides the minimum requirement is advisable in the following conditions:

- 1 Malnutrition and starvation
- 2 Conditions involving the growth, development or repair of tissues (Lactation, infancy and childhood, convalescence, pregnancy)
- 3 Prolonged or wasting illness (typhoid, chronic infections, tuberculosis, anemias, blood dyscrasias)
- 4 When the total metabolism or total food intake is increased (high caloric diet, hyperthyroidism)
- 5 Chronic gastro-intestinal disorders (gastric atony, constipation, colitis, ulcer, visceroptosis, sprue, pellagra)
- 6 Restricted therapeutic diets (diabetes, obesity, low residue, ulcer, ketogenic diets)
- 7 Some skin diseases

Vitamin deficiency may be due to many causes. The most important cause is inadequate or improper food intake. The vitamin is taken in with the food and undergoes some change in the gastro-intestinal tract, and is absorbed and taken to the liver by the blood stream, where other changes occur. These are necessary so that the vitamins may be readily utilized by the cells of the body. It can easily be seen that vomiting, diarrhea or anorexia, would allow inadequate vitamin-containing substances to be present in the gastro-intestinal tract for an adequate amount of absorption. The diarrhea may be due to frequent catharsis, idiopathic steatorrhea or sprue, or ulcerative colitis. Absorption may be diminished also, in any illness which changes the character of the absorptive surface, such as polyposis, ulcerative colitis or sprue. Then again the liver processes and stores some of the vitamins. Any serious disturb-

ance of the liver itself will disturb the vitamin content of the body and produce a deficiency.

It is almost certainly true that some bodily states require more vitamins than others, especially those conditions that require the growth, development and repair of bodily tissues (pregnancy, lactation and convalescence from illness) and also where there is an increased metabolism of tissue (hyperthyroidism). Then there is also an often unrecognized cause of deficiency which will be discussed in some detail later in this paper, these consist of toxins no matter from what source, whether they are bacterial or drugs tend to increase the need for vitamins and some of the vitamins at least, have a protective action against these toxic substances.

Let us rapidly review the early signs of some of the vitamin deficiencies. Early Vitamin A deficiency manifests itself as night blindness and dryness of the skin. In the eye, the regeneration of the visual purple is delayed, the eye becomes increasingly insensitive to light and night blindness ensues. Since considerable Vitamin A is stored in the liver in people who are well nourished, it is unlikely to cause much difficulty unless the patient has been ill for a long time. Vitamin B complex deficiency, on the other hand, is quite a different matter. The content of Vitamin B₁ for example is low in some of our best foods, i. e. liver and beef. Also, since the vitamins are water soluble, there is a heavy loss in diarrhea. There is very little disposition of the body to store any of the B vitamins. Since these vitamins for the most part occur together, it is most common to find multiple deficiencies, but an attempt will be made to break down the various states for didactic purposes.

Thiamin, riboflavin and nicotinic acid are all considered to be important enzymes in carbohydrate metabolism. Thiamin deficiency causes the well known conditions of dry and wet beri-beri, but these are far advanced states and rarely concern us. The conditions that are sometimes found in this country due to marked Vitamin B₁ deficiency are the so called alcoholic and pregnancy polyneuritis, and an interesting dilation of the heart with cardiac failure, called beri-beri heart. Williams, Mason and Wilder (1) deprived twelve cheerful and cooperative workers of thiamin in their diet for approximately ten weeks. They showed gross changes of behavior, marked changes of attitude, no inclination to do customary tasks and an inability to make social adjustments. They became irritable, sensitive to noise, and lost their manual dexterity. A half milligram to one milligram of thiamin per thousand calories of food brought about great improvement in

* Lecture delivered on May 17, 1943 in a Postgraduate course in Gastroenterology sponsored by the Kings County Medical Society and under the charge of Dr. Samson A. Seley. This lecture forms the basis of a chapter in a monograph by the author entitled, "The Diet Therapy of Disease" (In Press).

the physical and mental condition of these subjects. The therapeutic implications of these symptoms are obvious.

Riboflavin deficiency causes abnormal redness of the lips, fissures at the corners of the mouth, and a vascularization of the cornea. It also produces a certain atrophy of the tongue which is said to be characteristic of this deficiency. However, at least one authority (2) states that he could not differentiate the glossitis of riboflavin deficiency from that of nicotinic acid deficiency.

Nicotinic acid deficiency causes diarrhea, glossitis, skin changes and mental changes. A very early sign of this deficiency is that the slightest stimulus produces an exaggerated response, i. e. taking of blood from the vein is complained of as severe pain which may continue for hours.

Vitamin C deficiency if fully present, results in scurvy. This is rarely seen, but sub-clinical deficiency is often present, either brought out by some infection, following an operation, or brought out by sensitivity to certain drugs. Following an operation a delay in wound healing may occur, since the principle defect in Vitamin C deficiency is a poorly developed intercellular cement substance.

Vitamin D helps in the absorption of calcium from the intestinal tract and prevents rickets. Vitamin E may be effective clinically, and has been used in such widely divergent conditions, as amyotrophic lateral sclerosis and repeated abortions. Its effect in both of these conditions is disputed.

Vitamin K is a recent significant discovery. It is widely distributed in many foods. However, it requires bile salts for proper absorption and requires them in adequate quantities. Following absorption, the liver cells turn Vitamin K into prothrombin. Biliary obstruction leads to prothrombin-lack because of the absence of bile salts in the intestinal tract. Liver disease would also cause a deficiency of prothrombin, because the liver would be unable to change Vitamin K into prothrombin. Faulty absorption of Vitamin K from diseases such as ulcerative colitis, intestinal obstruction, and idiopathic steatorrhea may also result in prothrombin deficiency.

Certain principles in the treatment of vitamin deficiency may be enunciated. Oral vitamin intake is advisable whenever possible, because the purified vitamins used for injection lack many of the factors found in some of the cruder forms used orally. Some individuals require more vitamins than others. Besides this fact, many authorities do not agree on the prophylactic and therapeutic amounts necessary.

It may be worthwhile to list here certain recent advances in the vitamin field. Chesley (3) recently observed that certain symptoms in some of his patients cleared up on administration of Vitamin B complex. There were epigastric distress, constipation, flatulence, starch intolerance, alternating constipation and diarrhea, fatigue, bloating, nervousness, anorexia, skeletal pains and sensitivity to specific foods. These were considered functional disturbances due to Vitamin B deficiencies. Obviously, organic changes must be ruled

out very carefully before assuming the more benign condition to exist.

Lapore and Golden (4) reported the following findings in describing the syndrome that they believed was due to Vitamin B complex deficiency.

Flat dextrose tolerance curve, abnormal small intestinal pattern in the X-ray, malnutrition, hypo or hyperchlorhydria, glossitis, dermatitis, and anemia. The roentgenogram of the small intestines in Vitamin B complex deficiency was further described by Golden. He found hypermotility and hypertonicity in the early stages, hypomotility and hypotonicity in the later states. There was abnormal intestinal segmentation, a scattering of the intestinal contents, and intestinal gas due to impaired mucosal absorption. Mackie and Mills (5) found that these roentgenographic changes have a definite diagnostic value, they parallel the severity of the disease, and they regress with vitamin therapy.

Vitamin C

It is questionable whether ascorbic acid deficiency has an etiological relationship to the formation of peptic ulcer. Peptic ulcer is not considered to be a deficiency disease per se, at least not that of Vitamin C. However, the importance of the vitamin in the prevention of hemorrhage, once peptic ulcer has been established, seems clear. Portnoy and Wilkinson (6) noted severe degrees of undersaturation of Vitamin C in persons that had bleeding peptic ulcers. Ingalls and Warren (7) believe it is important to make certain that peptic ulcer patients receive adequate amount of Vitamin C. This deficiency was especially noted in patients with peptic ulcer that were given alkalis. They also considered the effect of the vitamin in the healing of the ulcer. Warren (8) recommends 200 mg of ascorbic acid daily for about 2 weeks. Others state that 1 to 3 Grams of ascorbic acid are usually required to correct the deficiency.

The effects of Vitamin C on adverse reactions to drugs are extremely interesting. The effect of ascorbic acid on the sensitivity to neoarsphenamine is well known, and has been repeatedly described (9). It is unknown whether the patients exhibiting the actions are deficient in Vitamin C, or whether Vitamin C detoxifies the neoarsphenamine in a well saturated patient. Recently, I described a case of rheumatic fever that rapidly became intolerant to salicylates and had a low ascorbic acid content of the serum, this patient was quickly relieved of his disability by adequate intake of Vitamin C (10). This was also shown to be true for several cases exhibiting intolerance to sulphonamides, and more recently to stilbesterol (11). These experiments remain to be further verified. They are certainly interesting if they can be shown to be true.

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THE VITAMINS—COUNCIL-ACCEPTED

Vitamins	Occurrence	Manifestations of Deficiency	Daily Requirements	Therapeutic Dosage
Vitamin A	Cod liver oil, halibut liver oil and other fish liver oils green leafy vegetables, yellow vegetables, liver, eggs, milk butter, apricots, yellow peaches, oranges and bananas	Nutritional night blindness Photophobia Xerophthalmia Certain type of hyperkeratosis of skin (dryness, scalliness) Pathology "Keratinizing metaplasia"	Adult 5000 units 3 ounces of greens or carrots 4 ounces of liver, Conserved in cooking	Recommended prophylactic dose equivalent of at least 2 teaspoonfuls of cod liver oil (minimum N.N.R. strength) but not more than 10 000 U.S.P. Units daily Larger doses may be necessary in treatment of deficiency states (10 000-40,000 units)
Vitamin B1 (Thiamine Hydrochloride U.S.P.)	Yeast, whole grains, (germ and outer layers of seeds), pork, liver, organs and muscles of many animals nuts, eggs, legumes and most vegetables Whole wheat bread is very important as good food sources are few	Beriberi Peripheral neuritis Cardiovascular disturbances Anorexia of dietary origin. Polyneuritis of alcoholism, pregnancy and pellagra.	Adult 1 to 2.5 mg Children .03 mg for each 100 calories. Infants .015 to .05 mg 4 oz. pork. Slight loss in cooking	10 to 50 mg daily in acute deficiencies.
Riboflavin (Vitamin B2)	Yeast milk liver wheat germ, eggs cheese, green leafy vegetables peas lima beans organs and muscles of many animals	Cheilosis Glossitis magenta colored, fissures common Seborrheic follicular keratosis (oil desquamation around nose) Vascularizing keratitis Photophobia, itching, burning, dimness of vision.	Adult 3 mg Infants 1 mg 4 oz. of liver 1 pt of milk requirements. Not destroyed by heat.	Suggested 3 to 15 mg daily
Nicotinic Acid (U.S.P.) (and Amide)	Yeast liver wheat germ bran, organs and muscles of many animals and several green leafy vegetables Milk is a poor source. Meats are not important common source.	Pellagra Characteristic dermatitis (sun burn like lesions on back of hands, wrist or forearms) Glossitis—Red colored Gastro intestinal disturbances Central Nervous system disturbances	Adult 20 mg Liver—1 oz.	Varies considerably An effective dosage is 500 mg daily in 10 doses of 50 mg each.
Vitamin C (Ascorbic Acid U.S.P.)	Oranges lemons limes tomatoes grapefruit fresh strawberries raw cabbage, green peppers and other fresh fruits and vegetables	Scurvy Prescurvitic Conditions—Loss of vigor, weakness, sore gums spongy gums	Adults 50-75 mg Infants 10-50 mg ½ grapefruit 1 orange 3½ oz. strawberries Destroyed by heat.	Adults 50 1000 mg daily Infants 30 100 mg daily
Vitamin D	Cod liver oil and some other fish liver oils eggs butter and milk Source other than fish liver oils contain too little to be practicable.	Infantile rickets Spasmophilia (Infantile tetany) Osteomalacia Abnormal dentition Abnormal calcium and phosphorus metabolism.	Adult 1000 units Children 400-800 units	Recommended prophylactic dose equivalent of at least 2 teaspoonfuls of cod liver oil (minimum N.N.R. strength), but not more than 1000 U.S.P. units Larger doses may be necessary in treatment of deficiency states Prematures 20 000 units daily
2-Methyl-1, 4-Naphthoquinone (Vitamin K action) (Menadi-one)	A pure chemical compound which exhibits marked vitamin K activity Has not been isolated from foodstuffs	Prothrombine deficiency Prolonged clotting time. Hemorrhagic diathesis in newborn, and in hepatic and biliary disease	Undetermined	1 to 2 mg

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OTHER POSSIBLE VITAMINS

Choline Considered to have function similar to that of vitamins Essential in fat metabolism

Vitamin H, or Biotin Prevents so-called "egg white injury" in rats A growth factor essential for yeast and certain microorganisms

Inositol Prevents loss of hair in mice Essential in fat metabolism

Para-Aminobenzoic Acid Reported to be a chromotrichia factor for the rat, and a growth factor for the chick and certain bacteria

Vitamin P, or Citrin A substance found in citrus fruits Reported to be associated with Vitamin C, and to be of value in maintaining normal capillary resistance and permeability

Vitamin B3 Concerned with growth and nutrition of pigeons Now believed to be pantothenic acid

Vitamin B4 Necessary for prevention of a specific paralysis in rats and chicks

Vitamin B5 Required for the maintenance of weight in pigeons Now believed to be Vitamin B6

Factor M A water-soluble, heat-labile factor, necessary for the growth of rats chicks and dogs

Anti-Gizzard Erosion Factor Gizzard erosion in chicks is believed by some investigators, to be due to a deficiency of a specific factor found in extracts of alfalfa, kale, etc.

Factors L1 and L2 Reported necessary for lactation in rats

Factor M A water-soluble factor found in yeast and liver that prevents oral lesions and pellagrie symptoms in monkeys (Courtesy Merck and Company)

NEWER VITAMINS—NOT COUNCIL-ACCEPTED

Vitamins	Occurrence	Manifestations of Deficiency	Daily Requirements	Therapeutic Dosage
Vitamin B6 (Pyridoxine)	Yeast liver, tikitiki rice bran, wheat germ and crude cane molasses	Significance in human nutrition not yet established Dermatitis in rats Anemia in dogs	Undetermined	Undetermined
Pantothenic Acid	Yeast liver and other tissues, wheat germ crude cane molasses, rice bran egg yolk, and wheat bran	Significance in human nutrition not yet established Dermatitis in chicks Hemorrhagic adrenals and chromatrichia in rats	Undetermined	Undetermined
Vitamin K1 (2-Methyl-3-Phytol-1, 4-Naphthoquinone)	Alfalfa, kale spinach dried carrot tops, tomatoes, fish meal, hog liver, soy bean oil and some other vegetable oils	Prothrombic deficiency Prolonged clotting time. Hemorrhagic diathesis in newborn, and in hepatic biliary disease.	Undetermined	1 to 2 mg
Alpha-Tocopherol (Vitamin E)	Wheat germ oil, cottonseed oil, and green leafy vegetables	Significance in human nutrition not yet established. Necessary to ensure normal course of pregnancy and to prevent paralysis in rat Necessary for normal growth of young rats	Undetermined	50 to 100 mg daily

A Modern Explanation of the Gastric Emptying Mechanism*

B**

J P QUIGLEY Ph.D

CLEVELAND, OHIO

THE mechanism of gastric evacuation is a question so intriguing and so important that as new techniques for studying the subject have become available, the subject has been reinvestigated. The emptying process undoubtedly can be modified (1) by variations of the force which attempts to expell the material from the stomach and (2) by changes in the activity of the pyloric sphincter which might prevent this expulsion. The relative importance of these two factors in the normal regulation of gastric evacuation has been variously stated. In large part, the different concepts proposed have varied as the investigational methods with their different advantages and disadvantages have varied.

For some years the studies chiefly involved a measurement of the fraction of the material introduced into the stomach which could again be recovered from the stomach or the rate at which it escaped from a high intestinal fistula. As a result of this very indirect approach to the problem, the pyloric sphincter was regarded as the structure through which the regulation of gastric evacuation was chiefly effected. The sphincter as "keeper of the gate" was believed to remain contracted most of the time and thus gastric evacuation was prevented (1). Some emptying was permitted each time the sphincter relaxed. The sphincter was believed to act contrary to or in opposition to the antrum, but in general the role played by the antral and bulbar motility in the emptying process was neglected or minimized. Investigations made with the X-ray or balloon technic gave results which did not strongly controvert the above concept and thus it persisted and grew in strength.

The regulation of the pyloric sphincter as "gate keeper" was ascribed largely to the concentration of hydrochloric acid. As popularized by Cannon (2), this theory claimed that when gastric contents were sufficiently prepared to be evacuated, acid accumulated on the gastric side of the sphincter. This caused the sphincter to open and evacuation occurred. However, when acid reached the duodenal bulb, it caused the sphincter to close and thus gastric emptying was temporarily prevented. Numerous investigators indicated serious objections to this theory, but until recently it continued to be extensively accepted.

A distinct advance was made when Thomas (3)

presented a clear exposition of the physical factors theoretically involved in gastric emptying. He placed particular emphasis on the importance of gastric pressure in the evacuation process and presented strong evidence that this pressure must be developed by antral peristalsis.

The chief factors normally involved in gastric emptying are indicated in the hydraulic model (Fig 1). The

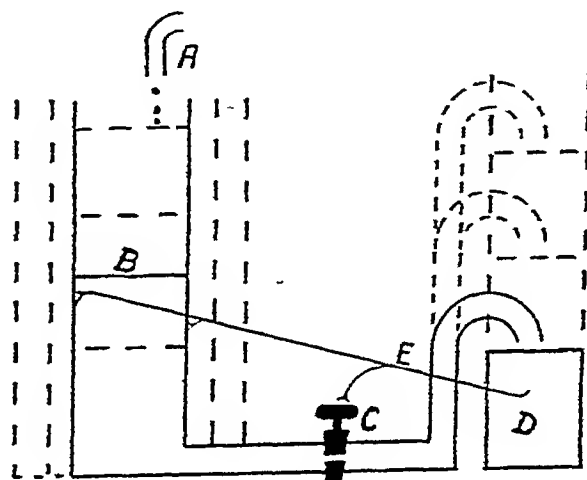


Fig 1

time required for emptying reservoir B depends in part on the amount flowing in from A (representing material secreted by the gastric glands or swallowed). A certain minimum hydrostatic pressure in B is essential to produce an outflow from this reservoir and higher pressures will tend to increase the emptying rate. The extent to which stopcock C (representing the pyloric sphincter) is open and the resistance encountered in discharging the fluid into D can also alter the emptying of B. Furthermore, an influence from D might act back through E to cause a relaxation of the walls of B with a consequent decrease in pressure head, or it might change the stopcock position.

Adequate investigation of a problem having so many variables requires a consideration simultaneously if possible, of each of its constituent parts. Conclusions based exclusively on the study of only one aspect, e. g. the rate of discharge of the material from a high fistula, may be quite erroneous.

Each of the factors here emphasized have recently received serious consideration and the results can be

From the Department of Physiology Western Reserve University Medical School

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assembled into a relatively complete "modern" explanation of the gastric evacuation process. The recent studies have used more direct methods than those previously employed and have shown that the pyloric sphincter is not closed most of the time. Wheelon and Thomas (4), Thomas and Crider (5), Meschan and Quigley (6) employed tandem balloons, Brody et al (7), Werle et al (8), Quigley and Read (9) used miniature sphincter balloons or observed the fluoroscopic shadow of shot stitched to the pyloric sphincter or recorded the shot movement with the pyloric diagraph. It was thus determined that the sphincter is relaxed most of the time, always when the antrum or the bulb is not displaying contractions and from 60-80 per cent of the time when the stomach is evacuating. Gibbs (10) obtained a similar impression from having observed the pyloric sphincter gastroscopically in 560 patients. He reported that "this structure remains open practically all of the time and closes only for a brief interval when the antral contraction wave blends with it."

After surgically eliminating the influence of the pyloric sphincter (pylorotomy, partial gastric resection, etc) the stomach frequently continued to empty in an essentially normal manner, (McCann (11), Shay and Gershon-Cohen (12)). Normal evacuation was also obtained by Crider and Thomas (13) and by Brody et al (7) when the stopcock action of the sphincter was eliminated by holding the sphincter open with a spool-shaped object having a 10 mm bore.

The recent investigations have rather definitely shown that the sphincter does not act contrary to the stomach, in fact, the entire pyloric region (antrum, sphincter and bulb) acts as a unit so that almost invariably the factors which increase or decrease the activity of one of these structures likewise alter the activity of the others in the same direction, although not necessarily to the same degree. When the pyloric region is at rest, all three parts are relaxed. The normal activity is cyclic and usually consists of peristaltic waves which involve in orderly sequence the antrum, sphincter and bulb.

Since gastric emptying is markedly influenced by the antral and bulbar pressures, the estimation of these values has received especial emphasis. A critical analysis of the balloon-water manometer technic (by Brody et al) demonstrated that it is incapable of registering pressure accurately. A method was then devised, suitable for the accurate and continuous measurement of antral and bulbar pressures. When applied to a study of the evacuation problem, these pressures were recorded during periods of gastric emptying. They were correlated by Werle et al with a simultaneous study of (1) the passage of peristaltic waves over the antrum and (2) over the bulb, (3) the passage of material through the sphincter and (4) the activity of the sphincter.

From these studies it was determined that gastric chyme passed into the duodenum only when a propulsive peristaltic wave passed over the pyloric antrum. Emptying was cyclic, e.g., emptying periods of 15 seconds duration might alternate with 23 seconds intervals during which no discharge occurred. During the first of the emptying interval, Evacuation Period A, antral and bulbar pressures were about the basal level (5-8 cm of water and 2-4 cm respectively). Thus a pressure gradient of 3-4 cm of water effected the initial part of the evacuation cycle. This moderate head of pressure sufficed to discharge gastric contents into the duodenum, for the sphincter and bulb were relaxed and offered but slight resistance. The antral peristaltic wave developed little antral pressure because of this low resistance to flow, i.e. R was small in the formula, $\text{Resistance} = (dv/dt) R$, where dv/dt is the time rate of volume change and R is the resistance to the escape of the contents from the cavity. Approximately 1/2-2/3 of the chyme discharged during a cycle passed through the sphincter during Evacuation Period A.

As the peristaltic wave involved the lower antrum, the sphincter began to contract, thus the resistance to the escape of antral contents increased and the pressure in the antrum rose to about 30 cm (Fig 2). During

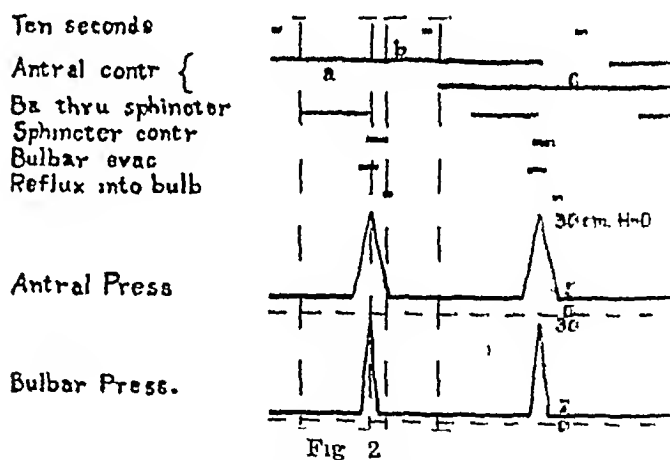


Fig 2

this interval (Evacuation Period B), the bulbar pressure remained near the basal level, so the antral-bulbar pressure gradient rose sharply and was able to maintain the emptying at about the previous rate. The emptying cycle terminated with all the chyme expressed from the terminal antrum and with the sphincter closed. The bulbar contraction occurred almost immediately, and since the sphincter was closed and the antral pressure was high, reflux to the stomach was prevented. Bulbar pressure rose to about 25 cm and forced the material down the duodenum.

The role of the sphincter in the evacuation cycle may be restated. During Evacuation Period A, the sphincter is normally relaxed and has but little influence on the passage of chyme into the duodenum. During Evacuation Period B, the sphincter is offering increasing interference to the egress of chyme. The effectiveness of this resistance must be significant, i.e., it holds back a moderate amount of material which otherwise

would be expelled. The magnitude of this effect has not been determined but certain of our records indicate that it is subject to some variation. Evacuation usually terminates when the sphincter is closed, but since the terminal antrum at this time has completely emptied itself, the sphincter is not essential in terminating the evacuation cycle. The period of complete closure of the sphincter overlaps such a small fraction of the interval during which the antrum is attempting to evacuate that the sphincter normally prevents evacuation for not more than 5 per cent of each cycle. The closed sphincter and a high antral pressure act together to prevent regurgitation of bulbar contents, for they both exist at the time the bulb is expressing its contents.

The effective evacuation pressure ($E \Gamma Pr$) is the pressure by which the antral-bulbar pressure gradient exceeds the evacuation resistance. During evacuation Period A, both the resistance and the gradient are low, but the $E \Gamma Pr$ is slightly positive and evacuation occurs at a moderate rate. Both the resistance and the gradient are rapidly increasing during evacuation Period B, but again the $E \Gamma Pr$ is positive and a moderate evacuation rate persists.

A variety of factors are known to modify the gastric evacuation rate. Many foods are believed to delay gastric emptying while still in the stomach (14) and to act by causing a firm closure of the pyloric sphincter. Quigley, Zetzelman and Ivy (15) showed that foods such as fats must be in the upper intestine to exert their retarding action. If the quantity of material (food, fluid or gas) in the stomach is enough to stretch the walls, gastric motility and evacuation rate are augmented (16, 17).

Foods such as fats (16), fatty acids (18), protein split products (19), hydrochloric acid (20), sugars (21), hypertonic solutions (22) when present in the upper intestine in naturally occurring concentrations and quantities or excessive quantities even of indifferent substances, retard gastric evacuation. This they do by causing a relaxation of the entire sphincter region, antrum, sphincter and bulb. The delay in gastric emptying does not result from a firm closure or spasm of the sphincter as was previously believed; actually it occurs in spite of a relaxed sphincter. The retardation in emptying is due to a suppression of the pumping action of the pyloric antrum. The inhibitory influence to the sphincter region results from the action of an inhibitory hormone (enterogastrone (15)) and an inhibitory reflex (the enterogastric reflex (23)) which originate in the upper intestine in response to the factors mentioned above. By means of this regulation of the gastric pumping mechanism, duodenal distention and the too rapid evacuation of irritating or improperly prepared food into the duodenum is normally held in check.

The literature contains many reports indicating that a spastic state of the pyloric sphincter is readily produced experimentally or clinically by emotions or by

noxious stimuli applied to almost any part of the body. It is also claimed that this pylorospasm is responsible for the retardation in gastric emptying unusually produced by such emotional or painful states. However, these claims were largely based on indirect observations or on experiments performed on anesthetized animals.

We attempted (24) to produce pylorospasm by emotional upsets, by agreeable or disagreeable stimuli applied externally, or by the distention of several parts of the digestive tract in normal unanesthetized dogs. The responses of the pyloric region were studied by rather direct methods. We observed that such procedures delayed gastric evacuation. However, contrary to previous reports this delay was due to a suppression of gastric peristalsis. Retarded emptying did not involve pylorospasm; in fact it occurred in spite of pyloric relaxation. These results indicate that the use of adequate investigative methods associated with a critical attitude will show pylorospasm to be a comparatively rare condition.

SUMMARY

Employing new investigative methods evidence has been obtained indicating that the entire pyloric sphincter region normally executes rhythmic contractions and tends to behave as a unit, i. e. the sphincter acts in a manner similar to, not contrary to the action of the antrum and bulb. Normal gastric evacuation is dependent on a pressure gradient from the stomach to the duodenum adequate to overcome the evacuation resistance. A study of the time relations of a pyloric sphincter region cycle shows that the pyloric sphincter is open much of the time and when open it offers little resistance to gastric emptying. The resistance offered by the sphincter while contracting is usually overcome by the increased pressure developed by the pyloric antrum. Reflux of duodenal contents is prevented by contraction of the sphincter and antrum. The presence of foodstuffs² or hydrochloric acid in the upper intestine retards gastric evacuation by depressing gastric motility. This retardation occurs in spite of a simultaneous depression of the sphincter and bulb. Emotional states or noxious stimuli also delay evacuation by suppressing gastric motility but not by producing pylorospasm.

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Tuberculosis of the buccal Mucous Membrane

By

AARON V WEINBERGER, M.D.,

NEW YORK NEW YORK

TUBERCULOUS involvement of the mucous membrane of the mouth is a rare manifestation of the disease, in view of the frequency of pulmonary tuberculosis and the abundant opportunities for autoinoculation with tubercle bacilli from the sputum. An analysis of approximately 5000 patients with pulmonary tuberculosis in the records of the Montefiore Hospital reveals oral involvement in about one and one-half per cent.

PATHOGENESIS

Tuberculosis of the mouth occurs (1) as a primary infection and (2) as a secondary manifestation to tuberculous foci elsewhere in the body.

(1) The primary form is theoretically possible through the introduction into the mouth of instruments, utensils, or food contaminated with tubercle bacilli. But for practical purposes this form can be disregarded. Many of the primary cases that have been reported, were found to have tuberculous foci in the regional

lymph nodes or in the lungs that had previously escaped recognition and in some instances the occurrences of an ulceration in the mouth was the first clinical indication, which led to the discovery of coexisting pulmonary disease. Primary tuberculous infection of the mouth is extremely rare.

(2) Secondary involvement of the mouth is the form usually seen and is commonly associated with the pulmonary form of the disease. This was the situation in the case reported herewith.

Oral tuberculosis occurs more frequently in men than in women to the approximate ratio of four to one for the reason that any predisposing local trauma is more apt to occur in men through chewing, smoking, etc., than in women.

The pathological varieties include the ulcerative, the milary and the infiltrative forms. The ulcerative variety is the commonest form of tuberculosis of the mouth. It begins as a collection of milary tubercles which



Fig. 1 Life size photo shows the F.B.C. ulcer and oedema of cheek and lip

castate and coalesce and leave shallow ulcers. Such ulcers are frequently seen in the buccal mucosa.

PATHOLOGY

A typical tuberculous ulcer of the buccal mucous membrane is superficial, with little or no infiltration or induration, is covered with a grayish exudate and has been aptly described as having a "moth-eaten" appearance.

The infiltrative form is rarely seen alone, ulceration being present. There is an associated oedema and pallor of the mucous membrane. This form is usually produced by an added mixed infection with other saprophytic or pyogenic bacteria.

As in all tuberculous lesions, the primary lesion consists of a closely knit collection of epithelioid cells with several typical giant cells in its immediate environment and with surrounding areas of round cell infiltration.

AVENUES OF INFECTION

In discussing the pathogenesis of tuberculous infection of buccal mucous membrane it is proper to consider the available avenues by which the organisms reach the site of the infection. The problem is whether such infection can be attributed (1) to a direct inoculation of the mucosa with the tubercle bacilli from the sputum, or (2) to circulatory transmission of the latter either by way of the blood or the lymphatics. The

current belief is that the circulatory route is the probable route of the invasion. This is, however, contrary to the previously held view that the direct implantation or inoculation is the usual method of infection. In either case it must be considered that there are certain inherent properties of the mucous membrane lining of the mouth that inhibit implantation and growth of the tubercle bacillus. These include the motions of the jaws, cheeks and tongue, the action of the saliva, the presence of other bacteria, and the nature of the tissues themselves, since striated muscles and stratified epithelium are known to possess a strong resistance to invasion by the tubercle bacillus.

DIFFERENTIAL DIAGNOSIS

The chief points in the differential diagnosis of tuberculous infection of the buccal mucous membrane are shown graphically in the following table.

TABLE I
Contrasting physical signs of four types of ulcer

	Tuberculous	Traumatic	Syphilitic	Neoplastic
Depth	Shallow	Varied	Deep	Deep
Color	Yellowish gray	Pinkish-yellow	Gray	Dirty gray
Edges	Smooth	Indurated	Ragged undermined	Raised and elevated
Sides	Sloping	Sloping	Yellowish-gray slough	Necrotic
Induration	Nil	Not marked	Resent	Marked
Pain	Very marked	Marked	None	Reterr'd pain severe
Local causes	Nil	Dental Caries, Etc.	None	Unknown
Other causes	Fissures, Sentinel Tubercles, Pulmonary T.B.	Nil	Leukoplakia	Nil

CASE REPORT

Patient H. J. Flower and Fifth Avenue Hospital No. 892-43 First admission, March 30 to April 19, 1943.

PRESENT ILLNESS

The conditions began two weeks before admission as a small ulcer of the buccal mucosa immediately posterior to the right corner of the mouth. Then the right cheek and right side of both lips began to swell and the patient had a moderate amount of pain which increased upon ingestion of hot food or fluids. There has been no tooth abscess or tooth-ache, so that the patient has not seen a dentist in a long time.

PAST HISTORY

Bilateral inguinal hernia with repair about fifteen years ago. Prostatectomy about nine years ago. Patient has shortness of breath on moderate exertion. No ankle edema. Nocturia once or twice nightly. Coughs

frequently and brings up a moderate amount of phlegm
No hemoptysis Smokes a pack of cigarettes daily

PHYSICAL EXAMINATION

The patient is a well developed elderly white man, sitting propped up in bed, coughing frequently and in no apparent distress There are no abnormalities of the head, eyes, ears or nose

Mouth Ulcer about the size of a dime on the inside of the right cheek near the corner of the mouth Ulcer is covered with a grayish membrane There are several smaller ulcers in the inside of right cheek The tongue is fissured There are many carious teeth and many teeth are missing

Neck Submaxillary nodes are palpable on right side

Thorax Normal to percussion Medium moist rales on the left side, most marked posteriorly

Heart PMI in 5th left interspace just outside of mid clavicular line. Sounds of fair quality Rhythm regular No murmurs or thrills

Abdomen Right inguinal hernia Liver and spleen not palpable No tenderness or rigidity

Consultant's Opinions

Dental consultation It was the opinion that the ulcer is the result of irritation from a razor like cusp of the upper right first bicuspid The right cusp is missing If the ulcer does not clear up within a week a biopsy is advised Also a full mouth X-ray was advised and taken to determine the necessity of any further extractions

GENERAL CONSULTATION

"The patient presents evidence of pulmonary tuberculosis, but this is not active at this time and does not seem to be a factor in the present condition About six weeks before his admission on March 30 there was a small lesion in the right side of the mouth On admission, he presented evidence of infection of the teeth, and all except two teeth have been extracted so that dental infection has been eliminated

Examination now shows an ulcerated lesion in about the center of the right cheek, the ulceration being about 1.5 cm in diameter with a well-marked leukoplakia covering not only the open lesion but extending beyond it on the mucous membrane of the cheek as far as the upper gum The lesion has a shaggy, hard base which infiltrates in all directions about 0.5 cm beyond the open lesion, especially towards the skin of the cheek There is considerable edema of the external aspect of the cheek and of the right-half of both the upper and lower lips, and there is a fissure at the right angle of the lips The mucous membrane of the mouth, otherwise, is free of evidence of infection except where recent sutures are evident in the gum in connection with the tooth extraction

"Decision of the exact therapy should await biopsy Large dosage of vitamin A with polyvalent vitamin therapy are recommended"

A biopsy was done, the report of which is as follows
Chronic Granulomatous inflammation, with tubercle formation and focal ulceration Tubercle bacilli present
Diagnosis Tuberculous ulcer

The dental examination was reported as follows
"The upper left second bicuspid has an area of infection at the root end The lower right first bicuspid has an area of infection at the root end There is a generalized alveolar resorption throughout the entire mouth Conclusions The alveolar resorption and the infected teeth may be acting as a foci of infection Recommendations Removal of all teeth except the lower cuspids"

The report of the X-ray examination of the chest was as follows Stereoscopic examination of the chest was made in the erect position at a six feet tube-film distance There is a collapse of the upper portion of the left lung The interlobar pleura is markedly thickened and prevents further collapse of the lung The right lung shows marked infiltration and fibrosis in



Fig 2 Localized pneumothorax in the left upper chest Diffuse mottling with fibrosis suggestive of caseous pneumonic type of pulmonary tuberculosis with a bronchogenic spread

the apex and infraclavicular region with fine mottled infiltration throughout the remainder of both lungs There are several highlights probably due to lipoidol and small areas of cavitation These findings are probably due to a caseous pneumonic type of pulmonary tuberculosis with a diffuse bronchogenic spread throughout both lungs

Conclusions Localized pneumothorax in the left upper chest Diffuse mottling with fibrosis suggestive of caseous pneumonic type of pulmonary tuberculosis with a bronchogenic spread

The laboratory reports are the following

Blood

Hemoglobin 87% 13.6 grams per 100 cc

Color index 0.91

Red blood corpuscles 4,800,000 per cmm

White blood corpuscles 12,600 per cmm

Neutrophiles—mature 63)
immature 12) 75%

Basophiles 1%

Lymphocytes 24%

Urinalysis

Color and appearance—orange—cloudy

Spec. gravity 1.030

Albumin—trace

Crystals—Many triple phosphates

Amorphous-Phosphates and carbonates

Ammonium and urate crystals Epithelia-Cellular elements decomposed by bacteria

CLINICAL NOTES

3-31-43

The sharp edges of the lower fourth, which probably caused the cheek ulcer, was removed in 2% novocain 4-7-43

Extraction of lower right and left first and second bicuspsids and right and left laterals

4-9-43

Under 2% novocain extraction of upper right lateral, left lateral and central upper left first and second bicuspsids and second molar

4-12-43

Under 2% novocain there was surgical removal of teeth Four sutures were used

4-15-43

Sutures were removed

On admission the patient's temperature was 101, which dropped to 98.8, then rose again to 101, remaining at that point for many hours. On the third day it was 99.6. Temperature was normal on the eighth day, and on the twelfth day, in the morning, it rose to 101 in the evening. Temperature reached normal on the eighteenth day, and on discharge it was 99.

Second Admission April 22 to May 5, 1943

The general examination of the patient is essentially the same as on first admission. Locally, the ulcer of the mouth is about the size of a dime with an indurated area surrounding it. There is a mucopurulent discharge. All teeth have been removed except two lower. Resonant coarse medium rales are present throughout the left chest anteriorly and posteriorly. Breath sounds harsh throughout.

On admission, the temperature was 101.4. On the third day temperature was 102, on one occasion, on the twelfth day it was 101.4, and on the day of discharge it was 99.4.

The essential parts of the treatment included multiple daily dressings by which the mouth condition was kept as clean as possible, the extraction of the offending teeth, and helio- and quartz light therapy.

After April 12, 1943, the buccal ulcer was treated

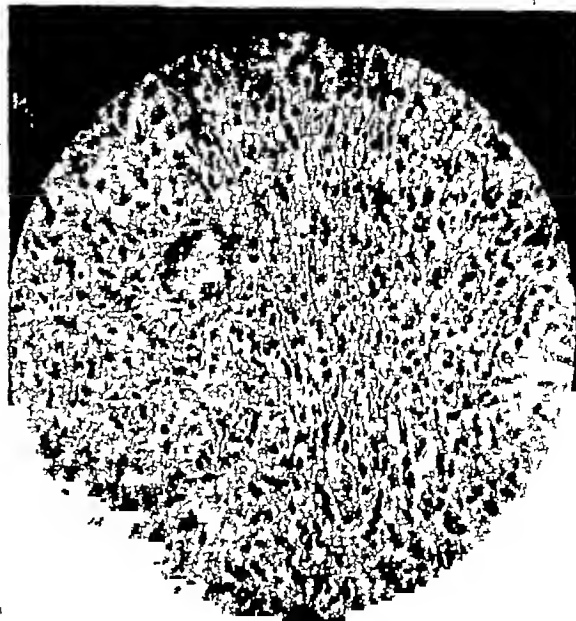


Fig 3 High power microscopic study of biopsy section shows stained acid fast bacilli among various tubercles

locally with sulfanilamide. This was incorporated in a fairly stiff base in a concentration of 5%. The stiffness of the base was changed by incorporating various proportions of pectin until the optimum consistence was obtained.* The jelly-like material was packed into the ulcer over a gauze packing and mechanically held in place for as long as possible, never less than several hours. There was no discomfort, nor complaint by the patient during the entire time.

After several weeks' use, the extraneous infection seemed to have disappeared from the site of the ulcer as evidenced by the disappearance of the infiltrated base. Then a smooth clean looking ulcer resulted. The removal of the extraneous infection is no doubt of great importance clinically, as the presence of the latter contributes almost entirely to the pain and discomfort of the lesion. The removal of the added infection is of great aid in the further healing of the ulcer. At the present writing the patient is still under treatment with this sulfanilamide preparation at another hospital. The ulcer is clean, non-indurated and shows some tendency to healing although this, because of the tuberculous nature of the infection, and the impossibility of any immobilization, is necessarily somewhat sluggish.

*This preparation was originated by Mr. Harry L. Wilensky of the Sulfu Drugs Products, 41 Union Square, New York City, who generously furnished as much of the sulfanilamide preparation as was needed. I am indebted to him for his kindness.

For Better Nutrition*

By

ALICE R. BERNHEIM M.D.

NEW YORK, NEW YORK

FOR the past fifteen years in the Clinic for Peripheral Vascular Diseases, we have considered the maintenance of an optimum diet an essential part of the treatment of our patients. Most of the patients on admission to the clinic were on diets markedly deficient in one or more of the substances necessary to proper nutrition. Of over 3 000 patients not one was on an optimum diet.

We stress the value of an optimum diet, first because in peripheral vascular disease with areas of diminished blood supply, the proper content of the blood in nutritive substances is relatively of greater importance than under normal conditions. Secondly, certain muscle cramps can be relieved by proper diet, and thirdly, the effect of an optimum diet on general health is obviously desirable. Accordingly our efforts were especially bent upon having patients carry out our dietary instructions.

We explained to our patients the importance of proper diet for their improvement. We gave them information, orally and graphically concerning the essential foods. We found that some followed these instructions but for the most part only sketchily and temporarily, and that in a few cases only was a continued, better dietary level achieved. Repeatedly given instructions were unavailing. We became thoroughly discouraged by our unsuccessful efforts to bring about optimum dietary regimens among our patients.

In considering the difficulties of the problem we realized the great resistance to change offered by established habits, prejudices, domestic arrangements and economic conditions. Also, advice to eat more vegetables, fruit, eggs, cereals, to drink more milk, seems to fall feebly upon the average individual since to him these substances are commonplace, and he does eat some of them to some extent at some time. In the back of his mind, he is under the impression that his diet is not much different from what you are telling him and that on the whole, it is fairly adequate. He is of the general opinion that he should eat what he likes and he is somewhat scornful of any other emphasis upon the choice of food. Apparently, education in this subject is a slow process.

We investigated our own dietary habits and found they were not an entirely satisfactory reflection of our knowledge of proper nutrition. We suspect further investigation among others who have knowledge of nutritional requirements would yield similar results. Obviously, knowledge concerning diet is not always sufficient to insure the establishment of optimum nutrition.

The choice of food for most of us seems to be determined largely by circumstance and only slightly by plan. Breakfast is commonly meager and hurried because of the rush to get to work or school. Luncheon usually consists of the offerings in sandwiches and pies of the lunch-counters or the ice-box. Dinner is usually the only planned meal of the day, and not always well-planned. The housewife nibbles between meals at home, children find candy easily available for their pennies and drugstores sell considerable quantities of doughnuts and coffee both in the morning and in the afternoons.

Lack of education in nutritional requirements and haphazard eating habits are definite obstacles to the establishment of optimum diets. Therefore we decided not only to try to educate our patients, but also to further the proper choice of food by a completely planned schedule. We now give our patients specific instructions. We tell them what food to eat and at what times it should be eaten. The general plan consists of three meals a day with intervals of at least five hours between them. No other food is allowed. These orders are modified, as far as possible, according to the needs, tastes and working hours of the individual. This method has succeeded where information alone had failed.

At the present time when the Food and Nutrition Board of the National Research Council is engaged in its widespread program of disseminating information concerning nutrition to improve the national health it seems pertinent to wonder how ready the response of well people will be to the educational campaign, in the light of our difficulty in establishing proper diets among clinic patients in a hospital.

Members of the American Association for the Advancement of Science have recently been asked to assist in the Federal Government's program of spreading information about proper nutrition. Concerning this request the following statement appears in the Bulletin(1) of this association. "Obviously there is an important problem before the country not only for the war period, but for all the future. How can it be solved, at least partially? Once illiteracy was widespread. It has been almost completely removed by universal interest in education and by generous support of little red schoolhouses all over the country. Evidently mass deficiencies of any kind can be cured only by mass activities. It is not expected that the members of the Association will undertake to become experts in the chemistry of nutrition. But it is hoped that they will assist in dispelling superstitions about diet, inspiring sane attitudes toward foods and disseminating elementary information about nutrition s m-

* The Department of Surgery, New York Hospital and Cornell University Medical College
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lar to that which, in recent years, has largely transformed the feeding of domestic animals throughout the country, often with astonishing results. The human problem is, of course, more difficult because there are prejudices to be overcome and economic problems to be solved."

Obviously, mass activities and wide dissemination of information were necessary to establish interest in education and to improve animal husbandry. But without regulated schedules could schools be maintained? Would the large-scaled improvements in the feeding of animals have taken place without definite instructions as to the necessary procedures? We are of the opinion from our experience that success in raising nutritional standards will be meager unless to general information is added more specific instruction. Even with full information it is apparently too difficult—too much of an effort—for the individual, especially in large cities, to plan a proper diet for himself. It is, however, relatively easy to follow a definitely outlined schedule. Our relatively small group (which might be called selected since, as patients, they were especially receptive to advice) did not improve their dietary standards to any marked degree on advice alone, and not until we outlined definite programs with regulated procedures did they incorporate a proper diet into the daily pattern of their lives.

Recently Carlson(2) has challenged the criteria upon which the national diet is judged to be deficient. He notes that knowledge concerning existing dietary standards is insufficient, and that signs and symptoms of early malnutrition are indefinite. Though these criticisms be true, nevertheless, the increase in well-being and general health which follow the adoption of an optimum diet by those whose diets have been considered fair may be called a therapeutic test of under-nutrition. As Sherman(3) has put it, an optimum diet makes for the difference between "passable" and "buoyant" health. The additional and more accurately measurable results found by Sherman in his feeding experiments with rats, i. e. earlier maturity, increased vitality, bigger and more vigorous offspring, greater resistance to infection and a ten percent increase in longevity unfortunately are data not yet available among human subjects.

If there is any doubt about the state of nutrition at large among well people, there is none concerning the dietary standards of our clinic patients whose eating habits as well as those of their families we have investigated. As stated above, none of over three thousand patients was on an optimum diet, and only rarely were the dietary standards found to be fair. Our standards for an optimum diet are based largely on Sherman's work, and on our own experience.

In recommending a definite dietary schedule for public use we are aware that modification according to individual tastes and idiosyncracies cannot feasibly be contained in the schedule itself. Apparently, our own schedule is easy to follow since modifications for the majority of the patients in our series have been unnecessary. At any rate because of the personal contact of physicians and patients such modifications are

readily made in a clinic. In general use, however, if for any reason either of dislike or hypersensitivity, an individual were unable to eat any of the required foods, substitutions could be arranged either by his physician or by dietitians in regional stations which could be established for that purpose.

Besides this possibility of improving general nutrition, there exists a large unused field in which definite dietary programs could be prescribed without objections. This large fallow field lies in the medical clinics of hospitals. For now, unless special diets are required, as in diabetes, peptic ulcers, etc., food habits are given scant attention by physicians in most hospital clinics.

We have examined many histories taken in medical clinics of large hospitals in order to find out how the matter of diet is handled. We have questioned numerous physicians from hospitals in other cities. From our evidence, we are of the opinion that were the National Research Council to arouse the interest and cooperation of physicians, in prescribing proper diets in hospital clinics throughout the country, it would acquire a large spearhead in its present crusade for the nation's better nutrition.

In the many clinic charts examined we found but one with a full dietary history. In otherwise well-recorded histories notations which deal with diet come under the heading of "Gastrointestinal Tract" and commonly are about as follows: "Appetite good. No food idiosyncracies. Tea 2-3, Coffee, 3-4, Alcohol, occasional." The paucity of the dietary history is exceeded only by the advice given as to proper diet, which is usually none at all. One especially well-taken history (diet excepted) stated that the patient ate a well-balanced diet. The symptoms of which the patient complained were cramps and fatigue in the legs. After treatment with thiamin chloride and arch supports without relief the patient was sent to our clinic, where the following procedure occurred:

Question, "What about your diet?"

Answer, "Oh, I eat a well-balanced diet."

So far our history tallied with that from the medical clinic. It will be seen, however, that further questioning failed to substantiate the patient's statement concerning his diet.

Question, "What do you eat for breakfast?"

Answer, "I have a cup of coffee and a roll sometimes two rolls."

Question, "Do you ever eat anything else for breakfast?"

Answer, "Sometimes when I have time I may eat a couple of eggs."

Question, "About how often do you have eggs?"

Answer, "About once maybe twice a week."

Question, "Do you ever eat fruit for breakfast?"

Answer, "Well, once in a while I may have an orange or some prunes but mostly I just have the coffee and the roll."

Question, "What time do you eat breakfast?"

Answer, "About halfpast six or quarter to seven."

Question, "When do you eat again?"

Answer, "About 10 00 o'clock I stop off and get a

cup of coffee and a doughnut or a piece of cake."

Question, "After that, when do you eat again?"

Answer, "About 12 30 I have lunch"

Question, "What do you have for lunch?"

Answer, "Usually I have a plate of soup, a sandwich, a piece of pie and some coffee"

Question, "What other foods are you likely to have for lunch?"

Answer, "Sometimes I have some spaghetti, once in a while some beef stew and potatoes"

Question "When do you eat again?"

Answer, "About 4 00 o'clock I have a doughnut or a piece of cake and a cup of coffee"

Question, "What do you have for supper?"

Answer, "Whatever the wife cooks"

Question, "What is that likely to be?"

Answer, "Meat, about three or four times a week, spaghetti sometimes, potatoes, some kind of a vegetable, but I don't like vegetables much"

Question, "Do you know how your wife cooks the vegetables?"

Answer, "No"

Question, "Do you drink any milk?"

Answer, "No"

Question, "Do you dislike milk?"

Answer, "No, the children drink milk, I just never think of it"

After this patient was put on a proper diet his symptoms disappeared in the course of several weeks

We have found that a full dietary history can be taken, instructions as to food requirements can be given, a definite regimen can be prescribed and modified according to need, and advice for the patient's family given as well in about one-half hour's time. We find this time well spent

COMMENT

Much still remains to be learned concerning proper nutrition. Not only are optimum quantities of some of the essential food substances not known, but a great deal less is known about their absorption. The question of the optimum number of daily meals for adults has received little attention. For infants and children, this important factor in the nutrition problem has been well and definitely settled. Nowadays in-

fants are fed every few hours from the very beginning of their lives and, shortly thereafter, some are fed only three meals a day. Practical experience and some scientific evidence indicate that a regimen of three meals a day for adults is also generally to be recommended. Booher(4) has recommended food between meals for factory workers with the claim that fatigue is lessened and vigor for work is increased. It would be interesting to know whether similar results could not be achieved with three adequate meals a day and some form of relaxing exercise instead of the extra feedings.

The question of the relationships among frequent feedings, intestinal acidity and absorption needs further study. Apparently, intestinal acidity increases as digestion progresses. Some substances, such as calcium and iron, since they are relatively insoluble in an alkaline solution, are best absorbed in an acid medium. Because frequent feedings tend to interfere with this progressive acidity, those foods which are poorly soluble in an alkaline medium would likewise be poorly absorbed.

SUMMARY

1 In our experience information concerning proper diet was insufficient appreciably to improve the level of nutrition among clinic patients. In addition, definite instructions concerning what food to eat and at what times to eat were necessary to achieve this result.

2 It is suggested that a definite dietary regimen be prescribed in the present campaign to better the national nutrition in addition to the general information now being disseminated by the Food and Nutrition Board of the National Research Council.

3 It is also suggested that considerable aid may be obtained by the use of medical out-patient departments of hospitals throughout the land as propagators of proper instructions concerning diet for patients and their families.

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Psychological Problems in Hypoglycemia

By

JOSEPH WILDER, M.D.*

NEW YORK CITY

THE subject of the importance of mental changes in spontaneous and induced hypoglycemia may be first illustrated by a recent case from this author's files. A young woman, after an operation for dermoid cyst of the ovary, complicated by venous thrombosis, etc., developed rather suddenly a severe psychosis atypical in character, coming closest perhaps to a kind of amentia. She had been confined to a mental state hospital and remained there about two and a half years. The correct diagnosis of "psychosis in somatic disease" was made, but except for a few routine tests nothing had been done to diagnose definitely the "somatic disease" she was suffering from. Taken to a private institution for that purpose she was found to have a fasting blood sugar between 45 - 60 mgm per cent and her sugar tolerance curve after 100 gm glucose was

0 - 1 - 2 - 3 - 4 hours

45 - 105 - 106 - 54 - 51 mgm per cent

The values of blood sugar during the day on a diet abundant in carbohydrates and frequent feedings by day and night, were on one day

109 mgm --- at 10 a.m.

83 mgm --- at 1 p.m.

52 mgm --- at 4 p.m.

108 mgm --- at 7 p.m.

On other days they fell as low as 31 mgm per cent (at 4:30 p.m.) Under a regimen very rich in carbohydrates, the patient, who was suffering from a real bulimia not only started gaining weight rapidly, but her mental condition began to show steady improvement although her blood sugar was still often at a deep hypoglycemic level. A further remarkable change in her condition took place with the institution of injections of a pituitary growth hormone (which is probably identical with Young's "diabetogenic hormone") after a period of 4 days, strongly reminiscent of Young's and Houssay's experiment in dogs, the morning values began to rise to 155, 97, 81, 87, 93, 68, 113 on different days. This improvement was interrupted after about 20 days by a sudden mental relapse accompanied by a drop in the morning blood sugar to 45 and 53 mgm per cent (again reminiscent of the typical "refractory" phase in Young's experiments). The injections were discontinued for 5 days in which the blood sugar rose spontaneously to levels as high as 181, 178, 120, 118 mgm per cent. After that time the injections were taken up again with single doses increased the morning blood sugar** showed then values of 88, 123, etc. On intermittent treatment the

morning values now remained 123, 140, 120, 122, 99, 115, 100, 104, 122, 118, 125, 120, 125, 130. The case still shows fluctuations in a very much improved mental condition and will be published when the observation is closed.

Here, the case is serving one purpose only to show that chronic psychoses may be caused by chronic hypoglycemia. It is obvious that such cases may remain "incurable" if not properly diagnosed and treated. If treated they might be cured. The case is not unique. This author and others have reported a number of similar cases.

In the past it might have appeared strange that neuropsychiatrists like this author and others, took a part in the description and publication of spontaneous hypoglycemia—an essentially internistic problem. The answer is simple: the symptoms produced by a drop in blood sugar are *mainly mental and neurological symptoms* and hence those cases, particularly the more severe ones, come more often into the office of a neuropsychiatrist than to any other specialist. We do not wish to let this opportunity pass by without mentioning a difficulty sometimes encountered in dealing with cases of hypoglycemia presenting more outspoken mental symptoms: medical hospital departments refuse to admit them because of their abnormal behavior, while purely psychiatric divisions sometimes declare themselves unable to cope with the intricate diagnostic and therapeutic problems of such a case. Only in the last few years the work done by Himwich and his associates (3, 4) on animals and on cases treated with Sakel's insulin shock therapy has enabled us to understand why the symptoms of hypoglycemia are mainly neuropsychiatric symptoms. It seems that the central nervous system holds a special position among all the organs of the body. Although containing fair amounts of glycogen it is unable to mobilize them as the need arises, to convert them into glucose like other organs. It is therefore completely dependent on the glucose supplied by the blood stream. If this supply is deficient the central nervous system loses its most important fuel: the intensity of the oxidation processes and the intensity of the nervous functions decrease and we can observe all degrees of diminished mental and nervous functions paralleling the level of blood sugar. This unique opportunity for objective study of mental functions of varying intensity is enhanced by the fact that we can restore these functions almost immediately simply by supplying the desired amount of glucose by way of intravenous injection. It is no wonder, therefore, that psychology avails itself of this unique opportunity never offered before. An additional opportunity to check up psychological changes in hypogly-

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** We are not using the term "fasting" blood sugar because the patient was never kept fasting longer than a few hours.

emia by objective methods lies in the fact that electroencephalography enables us to follow graphically the changes in the pattern of brain waves accompanying the psychological changes associated with the rise and fall of blood sugar (see Fig 1)

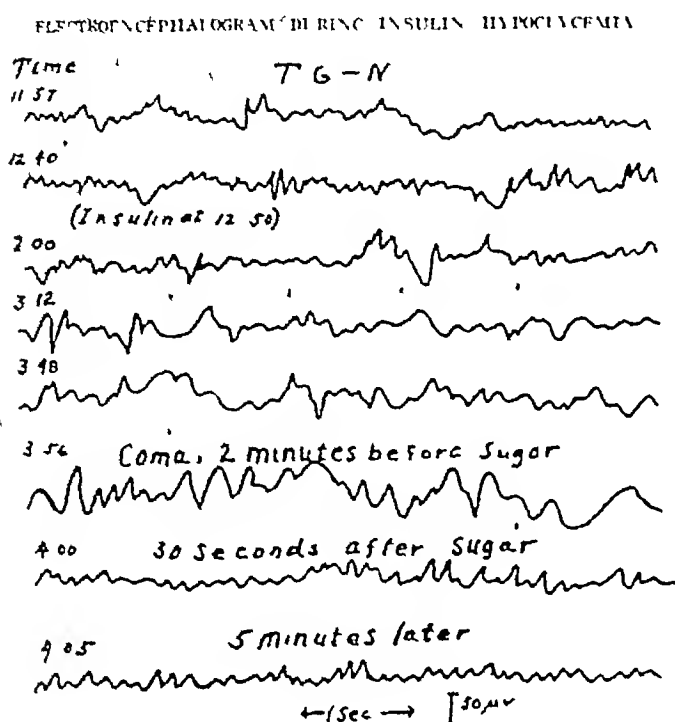


Fig 1 Oscillograms during an insulin treatment. Note slowing of alpha frequency and increase in number of long waves as coma is approached. Note also disappearance of long waves immediately after sugar and that the base line is then more stable than before insulin. From H Hoagland C S Amer J Physiol 120:559 1937 (5)

We have learned and are still learning more and more about the *causes* of hypoglycemia: insulinomas of the pancreas, diseases of the liver, adrenals, pituitary (13), etc., and last but not least diseases of the brain. To discuss this is not within the scope of this article. We wish to emphasize, however, that there also exist glycopenic conditions which might be occasionally provoked into manifestation by external causes; they are very frequent and the neuropsychiatrist ought to know them at least as well as a general practitioner, for they may be easily mistaken for neurosis. Examples are glycopenia of big eaters, or alcoholics, or in women who persist in combining weight reducing with sport activities, in Marathon racers, golfers, etc.

We regret not being able within the narrow limits of this article to give a *systematic* and comprehensive outline of the psychological symptoms of hypoglycemia, as we have done elsewhere (12, 13, 15).

The observations made in this field are based on

- 1 Cases of accidental hypoglycemia caused by an overdosage of insulin,
- 2 Cases of schizophrenia and other conditions treated with Sakel's insulin shock therapy,
- 3 Cases of spontaneous hypoglycemia caused by various ailments or conditions.

4 Incidental or experimental self observations by physicians and students.

We may mention here that even in *animals* we may observe most interesting behavior, negativism, emotional changes, apparent hallucinations, etc., not enough appreciated by the science of animal-psychology. In describing the clinical syndromes we shall use Sigwald's (8) classification. Sigwald differentiates between three forms of glycopenic attacks: the minor, medium, and major attack. Any one of these attacks may occur by itself, or progress into the next-severe form, unless it is previously counteracted by sugar application. The symptoms present in these attacks are rather manifold. We (15, 17) have grouped them into autonomic, cerebrospinal and mental symptoms, but in reality they usually appear in a combination. The *small attack*, for instance, consists mainly of autonomic symptoms such as hunger, perspiration, vasomotor manifestations, etc. at the same time, we usually observe mild psychical changes, such as irritability, difficulty in concentration, etc., cerebrospinal symptoms, such as double-vision or positive phenomenon of Babinski, appear but seldom in the small attack or may be completely absent. As regards the *medium attack*, the mental and cerebrospinal symptoms are much better marked: aphasic disorders, disturbances of sensibility, twitching, occasionally associated with dreamy stages, psychotic reactions with subsequent amnesia, etc. In the *major attacks*, we observe coma, sopor, stupor, epileptiform states, also chorea, hemiplegias, loss of control over bladder and anal sphincters, etc.

If we embark upon an illustration of these psychological symptoms, we will have to bear in mind that we have here an artificial isolation of symptoms and that we purposely disregard the more or less severe bodily symptoms which mark the attack. The psychological changes observed during the attack may be grouped into *typical* (such as are found time and again in the attacks), and *atypical* (such as are found in individual cases only). The manner of mental reaction is usually characteristic for one and the same person, but there exist exceptions, as well. So far we have not succeeded in finding any relation between the form in which a psychical reaction appears, and the *personality type* of the patient. Frequently we find the statement that the individuals in the respective cases had at all times been completely normal.

Minor attacks. It is not necessary that the typical psychical changes, occurring in the small attacks, must be fully developed. They are more or less in a parallel to such bodily symptoms as fatigue, hunger, perspiration, tremor. We mention above all in the realms of *consciousness*: a mild dullness, in the realm of *thinking*: a weakness in concentration and a mild hampering of the thinking process, in the realm of *volition*: a marked difficulty in making decisions; reaching up to complete abulia, in the realm of *mood*: frequently a depressive or anxious mood, occasionally also a marked irritability and opposition. Abulia on the one hand, negativism on the other, are responsible for the fact that frequently even patients who are familiar with the nature of their condition and who are obsessed

by the intense hunger sensation, cannot get themselves to accept the sugar, and rather change from a small attack into a more severe form, at times even becoming unconscious.

It might be interesting to quote a few fragments derived from auto-observations in such a small attack made by normal individuals in the insulin test (Wiedeking 9). A test-subject, at 7 15 a. m. on an empty stomach, is given 20 units insulin per intramuscular injection. During the following 40 minutes she is entirely normal, reads a medical textbook. Then there are bodily symptoms: excessive hunger, thoracic oppression, palpitation, tremor, etc., which symptoms, in the course of the following three hours, alternate from decrease to increase, and vice versa. Twenty-five minutes after the onset of the symptoms, the patient states that it required enormous will-power to merely shift her arm from one position into another. One hour later, this lack of will-power is much stronger. She says: "I don't want to move or talk. To take a pencil from a table requires as much will-power as climbing a mountain." When talking, her speech becomes dragging, difficult words require a repeated try until they are pronounced. The answers appear well prepared, but they come slowly. Various psychological tests show negative results. As soon as sugar water is used, the symptoms vanish immediately.

In this case absence of will-power, *abulia*, controls the picture. We find all of these symptoms much more marked in the *medium attack*. The medium attack usually develops from the small attack more or less rapidly. Its symptoms are of a much wider variety; here, we find more often interesting, atypical psychical phenomena,—again without any obvious relation to the normal personality of the patient. While the small attack consists mainly of autonomic manifestations, in the medium attack cerebrospinal focal symptoms reach more and more into the foreground, where the well known manifestations of double-vision, vertigo, ataxia, paresthesias and disturbances of sensibility, aphasia of different forms, appear associated with *striopallidary symptoms* of a varying character. Those strio-pallidary symptoms are of special interest to the psychologist because they often affect the *apparatus of vocal, mimic and gesticulatory expressions*, they may quite easily give the *false impression of psychological phenomena* while they are nothing else than motor manifestations. The attentive observer will often find that the expressions are either a little more inhibited or exaggerated than usual. Lid motion either stops completely, or there is increased blinking, at times there is a flow of tears, the facial expression turns rigid, or vice versa, the patient talks with excessive gesticulation, and makes faces, gesticulation may also stop entirely or become exaggerated, frequently, the patient will present continuous winding motions with his arms which remind one of affected embarrassment. Mannerisms are frequent, they are rendered more impressive by the *changes of speech* observed as slow, stuttering, indistinct, drawn, arhythmic, explosive, scanning speech, etc. The speech would come closest in comparison to that of a drunken man. There might also be different forms

of *aphasia*, with a special inclination towards perseveration, that is the automatic repetition of words or sentences. In rare cases there might occur *echolalia*, that is the echo-like copying of what the patient has heard, or *palilalia*, that is the compulsive repetition of any given word or syllable for some time. Frequent changes of *voice* also contribute towards the formation of such pseudo-psychological pictures, the voice becomes low or even completely aphonic, or loud and trumpeting—a symptom which we (10) have described as "megaphonia" in lesions of the corpus striatum. Strength and pitch frequently change. Even the legs participate in these expressions: an impatient stamping or tripping is often observed, which might progress into a continuous unrest of the feet, in one of my cases which on autopsy revealed particular damage to the corpus striatum this "dancing fit" lasted several days manifesting a kind of "jitterbug center" in the brain. How do we know that with these phenomena which so frequently furnish an impression of fear, irritation, hysterical theatricals, etc., we are dealing with purely *motor* manifestations which are completely separated from the psyche? Well, above all, the patients themselves gave us excellent information on their mental state during the attack, then we have frequently seen this mimic unrest, the manual gesticulation, etc. when the attacks take a turn for the worse, flow over into the picture of a chorea or an epileptiform attack etc., and continue in the *unconscious* state.

We have dwelt a little longer on those "pseudo-psychical" manifestations in the medium hypoglycemic attack, because they are so misleading. If we now return to the genuine psychological changes we must keep thinking of the *small attack*: hampering of thinking, concentration deficiency, mental dullness, lack of will-power, irritability. In the *medium attack*, this usually develops into more severe changes. In the realm of *thinking* there is a grave lack of thinking power marked by an arrest of thought along with the impossibility of fixation, near impossibility of a grouping, collecting, abstracting work of thinking, frequently reaching proportions of almost complete absence of concentration capacity and milder disorders of the sense of space, time, situation, and of consciousness such as mental dullness, longing for sleep. In the realm of *will-power*, the absence of the capacity to make even minor decisions is rather marked, and in a peculiar way contrasts with the obvious over-activity which is simultaneously present: a feeling of depersonalization is not infrequent, the *mood* is usually controlled by apathy and indifference which strikingly contrast with the—frequently simultaneously present—irritability. In the medium attack, this may increase up to an absolute negativism, an opposition against everything a querulous aggressive behavior which is also directed against the physician, and which is intensified by the mildest form of reproach. One of our patients offered backtalk before a sentence was finished, before she could possibly know what was wanted of her. The physician is constantly accused. Whatever he does is bad. This attitude finds its main expression in a refusal on the patient's part to accept the sugar or permit the doctor

to give him an injection. This refusal is often supported by force. This behavior stands in contrast to the fact that they know quite well that refusal to accept the sugar causes definite danger to themselves. Even when they are alone and have sugar with them they frequently abstain from taking it, occasionally because of the inability to arrive at a decision, then again because they suddenly have an oppositional thought against the consumption of the sugar. One of my patients, a case of spontaneous hypoglycemia, during an attack would claim that she had *diabetes*, and could consequently not eat sugar. One of Oppenheimer's patients, (6) a diabetic who had been treated with insulin, kept repeating during an attack "I am definitely not hypoglycemic! I am definitely not hypoglycemic!" It is interesting to note how in this stage there originate at times paranoid delusions of being wronged and persecuted, which vanish again. But this interesting speed-motion film of a rapid development of a change of character and personality is overshadowed by the unforgettable impression furnished by the rapid return of the original personality following the intake of a small quantity of sugar. Within minutes the storm subsides: the facial expression once again becomes placid—the old familiar, friendly, grateful patient has returned. It frequently happened to us in one of our female cases that in the waiting-room the patient was noisy and excited so that other patients were afraid of her and the noise would penetrate into the consultation room. In such cases the nurse would hand her a few pieces of sugar, and when the patient entered the consultation room, she was again the friendly, well-behaved lady she had always been.

We wish again to supplement this by some facts from an auto observation of a normal test-subject in a medium attack who had been given 60 units of insulin on an empty stomach (9). Leaving aside all bodily reactions these were the observations made. Three quarters of an hour following the injection there were elementary hallucinations which were not at all rare in this—and even more in the severe—attacks. The test-subject observes four strikingly yellow circles in the black of the eyes which after a while change into a bluish green, and subsequently disappear altogether. Fifteen minutes later, certain light experimental tests of action have to be abandoned because of striking fatigue. The mental condition is that of a dreaming state, occasionally, however, the test-subject may speak quite clearly to the nurses, and professes to feel well. She continues in that twilight process, but reacts promptly to a call and gives clear answers. In the third hour following the injection she states that there are noises in the adjoining room which she considers rather disagreeable, becomes irritated, claims that she cannot sleep because of these noises. In the fourth hour the twilight process becomes deeper and deeper, she says "This is funny, but I recognize you." She refuses to accept sugar water. Half an hour later she says "Now I begin to see clearer. I had a feeling as though I had passed over. What a strange situation. You are partly here, partly far away. Everything is seen and heard

like behind a veil. I experienced an incredible indifference to everything."

Josepha Wiedeking is justified in claiming that the *mental fatigue* of which her test-subjects complain is wholly different from the physiological fatigue experienced after mental work. There is a state of enforced waking, despite all desire for sleep the individual is unable to yield. Some of my patients searched for a word to describe that wide-awake state, one called it "bright-awake." As regards the disorders of the thinking process, Wiedeking's test-subjects claim that they were much too tired and dull to arrive at a definite thought. One notices what it is they are lacking: *activity, spontaneity in thinking*. It would seem that the very same fundamental disturbance of the initiative is to be held responsible for the anomalies in the mood. Predominant is an *intense absence of impetus* toward any form of activity. Thus, everything is just empty, dull. There are signs of depersonalization. If, in spite of this and that of deep indifference, we occasionally notice a slight impetus towards activity, it is abandoned soon again. We do not believe however that Wiedeking is justified in explaining the symptom of irritability merely out of a desire to be left in peace although we all know that a super-fatigued individual is quite irritable. Some points in the outward behavior of these patients, for instance their permanent conflicts with the police, etc., may be partly explained by the peculiar *indifference* which so much reminds one of that displayed by the alcoholic. A normal test-subject states "I do hear the voices of the nurses, etc., but it is just as though I were excluded from my former life. I feel absolute indifference. I register all I hear without adopting any special viewpoint. There are neither agreeable nor disagreeable memories." This striking loss of associations and associative power may also account for some of the mental changes. One test-subject states that she remembers having had a certain thought which, when normal, would have been embarrassing to her, while now that distinct sensation of shame (the thought concerned a forgotten obligation) was entirely absent. We shall discuss these moral changes later when we come to the chapter *Crime and Hypoglycemia*.

The *severe attack* presents heavy cerebrospinal symptoms that is, those of paralysis and irritation along with a wide variety of very severe *mental* changes, which here we can enumerate but briefly. The three most typical forms are *sopor*, *stupor*, *coma*. A severe state of shock, irreversible by sugar may originate, also epileptiform spasms, chorea, catatonic states, hyperkineses of various forms. Some of these are peculiar: a deep lethargic state may develop in which all bodily functions are enormously decreased, where the pulse is hardly perceivable, where respiration can hardly be observed, and so on. All this tends to remind one of hibernation, or suspended animation. Of interest are also the states of complete akinesia which originate out of a completely absent motion impetus. We seldom obtain information on these states during the state the patient is unable to talk and afterwards he is usually completely amnesic as regards this particular

period. Usually, these states are mistaken for complete unconsciousness. However, they remind one rather strongly of those cases of *apparent death* in which the patients also see and hear everything without being able to move. We have also various forms of hyperkinesia. One patient may knock at his bedstead for hours, another keeps pouring coffee over his head with a spoon, etc. Various clownish acts occur quite frequently, they are in a strange opposition to the otherwise normal behavior of the afflicted. For instance, a dignified merchant makes a sudden endeavor to juggle oranges or turn a somersault. Adlersberg (1) Then there is psychomotor unrest which may increase up to a wild, maniacal impulse to talk, run, move, or destroy. Often we observe mental automatism which reminds one of epileptic twilight conditions and fugues. Here, the most varied impulses appear such as a desire to wander or run, also homicidal and suicidal actions have repeatedly been observed. Of course all of these states are usually associated with a subsequent amnesia, and may be easily mistaken for hysteria, epilepsy, pathological intoxication, pathological emotion, simulation. But there are other psychotic pictures too: delirium, dementia, the Korsakoff syndrome, mania, melancholic depression, paranoid-hallucinatory pictures. Frequently, these conditions remind one of hysteria: there is not only the Ganser type of nonsensical replies, but also classical hysteria-like attacks with opisthotonus, *arc de cercle*, etc. However, these pictures always include also some atypical features. The hysteriform attack in hypoglycemia shows how organic and mental symptoms may be closely interrelated and how little we know about it, for instance *opisthotonus* is often the only and the classical symptom of hypoglycemia in the animal. In man, too, it may be an early symptom even in milder attacks. It is a well known fact that in the insulin, the electric and the metrazol shock there is frequent occurrence of vertebral fractures which are explained by the overextension of the spinal column in the epileptic attack. However, time and again we stumble over cases (also in the literature) where in a relatively mild twilight state the patient became conscious of the fact that he had to hyperextend his back while walking to such an extent that after the attack there would be a severe backache. The patient, however, definitely had neither an hysterical nor an epileptic attack.

One case taken from our own protocols may demonstrate to you just what peculiar psychological processes may occur in a severe attack. One of our female patients, a case of spontaneous hypoglycemia (13) at 8 in the morning while still in bed presented a certain motor unrest, she kept fumbling around, kept touching her lower lip and the left side of her head, etc. Her mental reactions were distinctly slowed up, replies to questions came but slowly and only after marked hesitation. Finally she changed into a state in which she lay motionless with her eyes semi-open, paying no heed to calls, and displaying hardly any reaction to pricks. Later on, she tried to get hold of the examiner in a manner often seen with hysterics: touched her genitals, the fingers kept fumbling the head was rhythmically

turned to and fro. We knew that we were dealing here with an acute attack of hypoglycemia because of the presence of muscular unrest, Argyll-Robertson pupil, positive sign of Babinski, incontinence of urine, decrease of blood pressure. Subsequently, the unrest subsided, the patient appeared as though she were asleep, and could even be awakened periodically. A metrazol injection did not change the state. As soon, however, as the patient was given an intravenous injection of sugar she opened her eyes while the injection was still being given, looked around, and said "Now I recognize everything, why was I not given the injection earlier? What time is it?" This patient had at that time received her very first injection of glucose and had positively no knowledge of the manner of disease which had befallen her. We may well assume that this was no typical unconsciousness, for no such rapid comprehension of the situation would have been feasible, but what state of consciousness she was in is hard to say, and difficult to study because this type of reaction is mostly followed by a state of complete retrograde amnesia.

We have tried to give above as briefly as possible a description of the more or less typical psychological changes of mild, medium and severe attacks of hypoglycemia in patients and normal persons. We have seen what changes are produced by a gradual decrease in intensity of mental processes. We have seen that those changes are more complex than one would assume, because the lessened intensity of higher functions leads not only to plain symptoms of mental deficit but also to peculiar symptoms of overactivity or—to be more precise—over-reactivity. It reminds us of phenomena we can see in applying the electric current to an incompletely damaged nerve. In discussing the above mentioned phenomena we consciously move more in the realms of the old descriptive psychology than in those of the modern psychoanalytical approach. In viewing these conditions in which the impairment of mental activity unquestionably forms the pivotal and essential disturbance, we cannot help thinking of older psychological concepts of Beard's irritable weakness or neurasthenia, of Janet's psychasthenia, of Berze's explanation of schizophrenia as a hypoactivity of the psyche. Those authors explained the symptoms of neuroses and psychoses on the basis of a lack of psychic activity and their treatment was stimulation of that activity.

The study of hypoglycemia opens new avenues to a tremendous number of psychological problems of theoretical and practical importance. The only thing we can do within the frame of this article is to pick at random some practical problems. We can choose e.g. some minor hypoglycemic phenomena to which we would like to apply Sigmund Freud's term of *psychopathology of every-day life* (*Psychopathologie des Alltagslebens*).

One, for instance, is the symptom of *dawdling*, which this author described on several occasions. It may appear in a patient but it may also occur in a person whom we do not suspect of hypoglycemia unless we have made a blood sugar test. A woman gets up every

morning, this being a favorite time for hypoglycemia and starts dressing, after a short while she interrupts this and begins to make the bed or clean up the room. Utensils and things lie scattered all over the room which presents the picture of a chaotic mess. This may take her hours. But let her have her breakfast and the patient and the room are in the usual orderly condition in no time. If we recall the symptoms of indecision, of quick spending of every initiative, of indifference, etc., we may come to an understanding of this peculiar phenomenon.

Switching from the wife to the husband, the man in question may be a good fellow but the wife knows that right before meals he is a changed man. With her better psychological instinct she would never discuss the purchase of the new hat with him before dinner. The rule "Feed the beast first" is a law in her home. And yet she knows nothing of hypoglycemia. Insulin and spontaneous hypoglycemia have actually several times caused divorce proceedings because of cruelty and other abnormal behavior of one partner. This author had to deal with a case of hypoglycemia with epileptiform attacks in which the following matrimonial situation developed. The wife maintained that her husband was the meanest, most brutal individual, he beat her up, mistreated her, etc., she was all her life puzzled by the fact that he was so popular with all the rest of the world who could not praise him enough, as a fine and nice man. This was the explanation the man woke up in the morning with definite hypoglycemia and was the bad man, he ate breakfast and left the house immediately after, hence, outside he was not hypoglycemic and a good man, toward evening his blood sugar began to drop and he came home mad as hell, unfortunately the poor woman was the only person who had practically never the opportunity to see him in a normoglycemic state.

Turning from the parents to the children we have to know that blood sugar in children is much less stable than in adults, hypoglycemia, especially the milder forms, is very frequent and shows interesting somatic and psychological peculiarities. Vomiting, epileptiform seizures, are much more frequent in children. Certain cases of somnambulism and pavor nocturnus have been traced back to hypoglycemia. Other disturbances of sleep may occur on this basis. Only a few months ago we could "cure" a case of stubborn enuresis nocturna in a 10 year old boy by some candy at bedtime. The good and well trained child who has temper tantrums just before dinner shows often on careful observation a slightly rigid expression of the face, a little blinking of the eyes, some pallor and perspiration. It is a pleasure to see how such a child who absolutely refused to eat would start eating with appetite after it had received some candy or chocolate. These are cases where the busy, old-fashioned mother who secured peace at home by a piece of candy was superior to the modern mother who would bring the child to a psychoanalyst. Although we have not yet collected such evidence we can easily imagine that wrong educational measures will produce a problem child where in fact we have but a problem in a child. We have not much but

some evidence that probably even a neurosis can be created this way. This evidence is derived from psychoanalysis of adult neurotics. Let us quote one of the very few examples from our experience. In treating a patient with a very severe compulsion neurosis we came to the conclusion that the fear of being insane and being rejected by people as insane was the core of his neurosis. The origin of this fear could be traced to his childhood. His family lived in Russia in the first world war at the verge of complete starvation. He remembers that he often would wake up at night, quite confused and screaming from hunger, he would even eat the chalk from the walls! And he remembers his family—very simple and religious Jewish people—discussing his condition and deciding that a demon (a "dybuk") must have entered his body. They all, including our patient, believed in this firmly and apparently all his compulsion neurosis had something to do with that idea of a demon in him.

Thus it is worth while to pay more attention to the possibility of hypoglycemia as the real trouble maker in family relationships. As a matter of fact after most of our lectures on the subject we had the pleasure of learning that one or the other of such family problems had been solved sometimes even in the family of the colleague who attended the lecture.

The case just quoted, of the "demon" in man, leads to another practical problem, known as the problem of "split personality," to which hypoglycemia furnishes most interesting contributions. Several times patients of this kind were characterized by their relatives as "Dr. Jekyll and Mr. Hyde." To discuss this, however, would unduly enlarge this paper.

A problem of great practical interest is given by the question as to whether frequent glycopenic attacks might lead to *lasting* mental changes. There is no doubt in our mind that this may actually happen. Distinct pathological changes in *cerebro* have been described repeatedly. In one of our cases we were able to observe this occurrence before the case turned entirely irreversible. Our patient who suffered severe glycopenic attacks almost every morning before arising, changed more and more into the picture of a paranoiac. She claimed poisoning and persecution, lodged complaints with the police, and was repeatedly confined as a paranoiac. It was very interesting to observe how, within ten days, without any psychotherapy, her paranoid ideas reversed rapidly as soon as she was admitted to the hospital where she got an adequate sugar ration.

Another interesting psychological problem is presented by a fact which is also of differential diagnostic importance. Hypoglycemia is the only condition which improves temporarily when the patient becomes *mentally excited*. This is easily understandable. Excitement is known to increase the blood-sugar. It thus happens that such patients will be rid of their attacks for many weeks following an operation, even if the adenoma had not been found or removed. One of my own patients, who for years had been suffering almost daily attacks, was rendered free from attacks for fully four weeks when her sister with whom she had been living

for many years met with death. When on the other hand one of her brothers died with whom she had entertained but little contact, she presented no improvement (14). Here, the blood-sugar, so-to-speak, was a measuring tape for her sisterly love.

However, the interrelationship with excitation is not so simple as that. Excitation is responsible for an increase in blood-sugar, in that it mobilizes the glycogen reserves in the liver. If this happens very often and it—as is frequently the case with excitement—the carbohydrate supply is inadequate then, after days and weeks there might develop a glycogen deficiency in the liver, resulting in a tendency towards hypoglycemia. Often the differentiation between psychogenic and glycopenic excitement is not easy. There are many little diagnostic signs which can be helpful. To mention but one: If we see a patient who is excited and shows bradycardia at the same time we ought to think first of hypoglycemia (provided it is not a case of heart block). These facts cause us to regard some of the pathological emotional reactions with a different thought in mind. The patient flies into a rage—spite and wrath prevent him from eating—a mild hypoglycemia might result which, in turn, influences his psyche again in the sense of increased irritability, thus, we have here a *circulus vitiosus* often leading to explosive or even criminal acts. Since we have acquired the habit of inquiring in the case of psychopathic reactions, when the patient has had his last meal, it has been startling to hear how frequently the emotional reaction had been preceded by an abstinence from food that lasted for 24 to 48 hours.

It is only clear that a neurosis which might happen to coexist, can utilize such a condition as well as any other. We have published such cases in the past (11). A woman who found herself in a terrible mental situation was undergoing a cure for weight increase with insulin in the course of the cure, there were repeated glycopenic attacks. These attacks kept recurring long after the insulin injections had been interrupted. The blood-sugar, however, remained normal, or slightly increased sugar had no effect, she responded to suggestion, etc. What we faced in this case was a hysterical pseudo-hypoglycemia which disappeared following psychotherapy.

Another example of the practical importance of the study of hypoglycemia is *crime*. This may sound surprising unless we remember how many psychological features we have found in hypoglycemia which might result in crimes and transgressions: not only the impairment of judgment and concentration, but also the imperative hunger, the absolute negativism, the irritability, indifference, impairment of moral sense, etc. Adlersberg and others (1, 2), have repeatedly published most interesting cases in diabetics treated with insulin while this author was more interested in the legally much more difficult cases of spontaneous hypoglycemia. In an article in the *Journal of Criminal Psychology* we (16) compiled a whole list of cases from the literature and our own experience of crimes committed in the state of spontaneous or induced hypoglycemia like *disorderly conduct particularly resistant against the police assault and battery attempted*

homicide and suicide, cruelty against children, like sticking a pin into a baby's eye (2), etc., matrimonial cruelty various sexual perversions and aggressions, false fire alarm, embezzlement, petty larceny wilful destruction of property arson, slander and the frequent violation of traffic regulations.

N. Rojas (Buenos Aires) has examined the blood sugar in about 130 delinquents shortly after their apprehension (7). In about one third of them the blood sugar was below 75 mgm per cent in some it was 50 and even below 40 mgm per cent. The "Legal Aspects of Hunger" is the subject of Rojas' report before the Pan-American Neurological Congress 1943. It is not necessary to stress that not every case with hypoglycemia must have symptoms. We would not even try to discuss this complicated matter here. But on the other hand we should know that not only in diabetics may hypoglycemic symptoms appear at normoglycemic or even higher levels. We had the following case under observation: a man had a long history of states of extreme excitement, violence, attempts of suicide divorce querulousness, etc., was several times confined in a psychiatric ward. The diagnosis was at times schizophrenia at times psychopathic character. His fasting blood sugar was 133 mgm per cent and he had never had glycosuria. Whenever his blood sugar fell below 120 mgm per cent he developed physical and mental changes typical of hypoglycemia. The same happened 2½ hours after an insulin injection at a blood sugar level of 110 mgm per cent. The symptoms could be promptly removed by sugar. The skin sugar curve did not show any marked abnormality as compared with the blood sugar curve. It seems that this patient, perhaps a potential diabetic was simply adjusted to a much higher level of blood sugar.

SUMMARY

The symptomatology of hypoglycemia, spontaneous and induced is chiefly neuropsychiatric in character. The study of various degrees of certain mental activities and their consequences opens new avenues to psychology and psychiatry. The knowledge of those changes is of great importance in many fields of normal life and particularly in medical practice. Some examples are discussed briefly.

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The Effect of the Liver Fraction of Duodenal Drainage on Certain Forms of Animal and Vegetable Life *

By

MARTIN E. REHFUSS, M.D.

and

THOMAS WILLIAMS, B.S.

IN a previous communication (1) we pointed out some of the physical and chemical changes to be noted in the fluid fraction of liver bile obtained by duodenal drainage. The therapeutic use of this procedure in many thousands of cases during the last twenty-five years has left one of us (M. E. R.) with the impression that duodenal drainage does something more than simply remove a small bile fraction or clear the ducts. Except in those inflammatory conditions of the biliary tract in which drainage may accentuate the symptoms, there is a resultant clinical improvement and a sense of well being which cannot be explained on a purely psychological basis. The appearance of the patient and the subjective relief afforded suggests that in certain instances detoxication has been achieved, leading us to believe that the removed bile has variable qualities.

The literature on bile toxicity is already voluminous and in many places contradictory, but the general opinion seems to be that the bile acids are the toxic substances. The early investigators (2), working with impure chemicals and drawing their conclusions from indirect work as from filtered bile, attributed the greater toxicity to bilirubin, and still others suspected the salts of bile. Horrall claims that the bile acids are toxic but that bilirubin is not. Certainly there is abundant evidence that the whole bile kills quickly when injected intravenously into laboratory animals, and that duodenal bile as studied by Antitch is lethal to rabbits.

Clinically one is amazed at the degree of icterus which is compatible with life, and by the extreme toxicity of bile and bile salts when injected intravenously in contrast with their relative innocuousness when ingested by mouth, even when the hepatic filter is seriously impaired. Equally impressive are the phenomena manifested by hepatobiliary sufferers, who, more than

any other digestive invalids, are subject to the toxic syndromes described in detail in the French literature (Parturier and others (3)). That there is a jaundice with an increase in pigment alone (dissociated jaundice) has been established (4), and that there may be normetric cholemia in which bile acids are increased but not the pigment in the blood is also conceivable (5). The experience of one of us (M. E. R.) tends to increase the evidence that the symptoms of cholecystitis have an underlying toxic basis—that the liver bile fractions are markedly dissimilar both physically and chemically.

We have, therefore, conducted this experimental study on the effects of bile obtained chiefly from patients presenting clinical and often toxic symptoms. In some cases the fluid obtained by duodenal drainage may be 20 to 60 cc per hour, in others, two or three times that amount. It may be clear, yellow and syrupy, or may show a diffuse yellow cloud due to admixture with gastric secretion. These differences in appearance and quantity, and other data, on each of the 138 specimens used were carefully recorded. After evaporation on the water bath their diverse physical characteristics were obvious. Some were almost black, others a light earthy color, some formed hard dry flinty masses, others were deliquescent, and still others sticky with what was thought to be lecithin. The observations on the color changes and variable chemical reactions obtained in tests on these dried specimens will be described in a future paper.

The first experiments in our series were performed upon small tropical fish, the common guppy, of which 3 were placed in each of six separate aquaria, together with a piece of the water plant ordinarily used by fish fanciers, and controls kept. Measured amounts of bile extracts were then introduced until the water was distinctly colored. Even after the lapse of a week all the guppies were still alive, but in almost all the aquaria

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containing bile solutions the water plants showed deterioration. This experiment was repeated with the same results.

We next employed *Daphnia pulex*, the common active water flea which is used as food for fish. Several separate cultures were introduced into a series of test tubes containing dilute bile extract using controls of daphnia in distilled water. In repeated experiments however we were unable to demonstrate any toxic effect of the bile extracts on the water flea after forty-eight hours.

The same procedure was again carried out using active cultures of mosquito larvae. These were placed in test tubes containing distilled water and various amounts of bile extracts, but in no instance could we demonstrate any lethal or toxic influence.

In surprising contrast, however another series of experiments demonstrated the vulnerability of freshly hatched tadpoles to bile extracts in dilutions of distilled water. The following illustrates the common experience.

		Observation after 8 hours
Control	Distilled water	Living
No 38	Bile (300 mg per 100 cc.)	Some living
No 5	Bile (300 mg per 100 cc.)	Dead
No 53	Bile (300 mg per 100 cc.)	Dead
No 47	Bile (300 mg per 100 cc.)	Dead

It was apparent that the bile salts interfered in some way with oxygen assimilation because the tadpoles rose immediately to the surface but gradually became less able to do so and finally sank to the bottom.

We then studied the effect of an oil solution on the animals. Five tadpoles were placed in each of a series of test tubes about two-thirds full of distilled water. Three quarters of a millimeter of mineral oil was placed on the surface of the fluid in one tube, and 2 cc. of a 1:5 dilution of whole bile was added to the others. The tadpoles in the mineral oil group remained active for twenty-five minutes, those in the bile group died in sixteen minutes. If death was due to interference with respiration, it is evident that the effect of the bile preparation was more rapid than that produced by covering with oil.

Our observations having led us to believe that a difference in toxicity existed, the question as to whether the same concentration of various bile extracts produced different killing effects was our next consideration. While a certain concentration of the majority of the extracts killed the tadpoles, the same concentration of others was notably weaker in effect. The following table illustrates the typical findings.

	5 min	Experiment No 49 8 min	10 min	April 3 1943 11 min.	3 Day Old Tadpoles 15 min.	16 min.	20 min.
Control							
No 38				One at bottom	None dead	None dead	None dead
No 48			Near bottom but moving	Three at bottom	One swimming	All at bottom	Four dead
No 53			Two at bottom	One dead, another dying	Only two swimming	Two swimming three at bottom	Two swimming three at bottom
No 5	Two at bottom	All at bottom	Apparently all dead	All dead	All dead	All dead	All dead

We then experimented with the addition of metallic salts to these solutions, and used for the purpose about 500 tadpoles two to five days old. The following protocol illustrates the general effects observed.

Experiment No 49 Begun 4/14/43 4:30 Observed at

	6 15	7 10	9 40
Control plus 3 gtt. Ferric alum	12 dead	1 alive	1 alive
Bile solution plus 4 gtt. Ferric alum	all alive	7 alive	1 alive
Bile Solution plus 3 gtt. Iron solution	1 alive	1 alive	all dead
Distilled water	all alive	all alive	all alive
Plain water	all alive	all alive	all alive
Distilled water plus 5 gtt. Copper solution	dead	dead	dead
Distilled water plus 5 gtt. Bile solution	dead	dead	dead
Distilled water plus 5 gtt. Bile and copper solution	dead	dead	dead
Distilled water plus 5 gtt. Bile solution	alive	dead	dead
Distilled water plus 3 gtt. Bile solution	alive	dead	dead

As shown by this experiment, 5 drops of the dilute bile solution was the killing dose for that particular bile. Several of the extracts, however, were found to be almost nontoxic, which strengthened our belief that there are relative differences in bile toxicity.

In searching the literature on this subject we note that Macht and Lubin (6), in demonstrating certain forms of toxicity with *Lupinus albus* seedlings found that bile pigments as such were not very toxic to plant

protoplasm, but that bile salts were, that solutions of either sodium glycocholate or sodium taurocholate in concentration of 1:10,000 killed the plants, that dilutions of 1:100,000 gave a growth index for sodium gly-

cocholate of 88 per cent with sodium taurocholate somewhat more toxic, and that even cholesterol, in suspension, had a slightly inhibitory effect. These authors prepared a chloroform extract of nail parings (according to the method described in the chemical studies of Una and Golodetz) and tested its toxicity on plants. It was found that even the small amount of oxysterol thus obtained produced a distinctly inhibitory effect on the growth of *Lupinus* roots.

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The marked depressive states of the nervous system exhibited by patients suffering from cholemia have been attributed to absorption of bile acids, and Macht (7) has reported the production of such depressive states by the injection of as little as 0.5 mg. of sodium glycocholate into rats, with sodium taurocholate exhibiting even greater toxicity. Macht and Hyndman (8) in their studies on the influence of bile acids on the cerebrospinal and neuromuscular reactions of rats, and on the effect of various decompositions of bile acids as well as of the bile acids themselves on the seedlings of *Lupinus albus* and *Vicia faba* showed rather convincingly that while glycine and taurine are comparatively nontoxic for both animal and plant protoplasm, cholic acid, on the other hand, exerts a very depressant effect on the neuromuscular and cerebrospinal reactions of rats in the circular maze and also on the growth of seedlings. They therefore attributed the toxic effect of the bile acids on animal as well as plant protoplasm to the cholic acid component of the bile acid molecules. Furthermore they found this compound to be extremely poisonous for certain forms of bacteria, namely the pneumococcus, which of course is a well known phenomenon.

During the winter of 1938-39 we conducted experiments in Florida on the effect of the dried bile extracts on zinnia and marigold seedlings, and found that unquestionably there was present a substance which inhibited the growth and in sufficient concentration, killed the plants. It was apparent that the toxic principle varied with each sample and occasionally an extract produced almost no toxic effect.

In the winter of 1939-40 we used the seedlings of bush beans, tomatoes and radishes, and in other tests spinach, carrots and Italian rye. The earlier seedlings were begun in moist sand, but the radishes were started between layers of blotting paper saturated with plant nutrient solution (9), finally we employed the nutrient solution alone, and all the plants grew very well.

In our early experiments we transferred the seedlings directly from the soil to the bile solutions. Realizing, however, the danger of injury to the delicate root systems we afterward fused a hole, by torch, in the bottom of each test tube and then suspended the seedlings, with their root systems intact, into the tubes which extended down into vessels containing nutrient media and later experimental solutions.

The leaves soon began to wilt and dry after suspension of the seedlings in dilute bile extracts, and respiration finally ceased, as attested by the fluid level. A healthy seedling will consume considerable fluid in twenty-four hours, if the seedling is dead the fluid level is affected only by evaporation (Fig. 1). The following is a typical observation: "February 20, 1940. Compared seedlings immersed for only three hours in the dilute bile solutions with those in continuous immersion for twenty-four hours. Those immersed for three hours in bile and returned to the nutrient solutions are not in as good condition as the controls. The leaves hang down but are still green, not shriveled or brown. The twenty-four hour immersion shows unmistakable changes, not as pronounced as in the marigold and zin-

nia because the latter were younger seedlings with only a second leaf, and these are older tomato seedlings (several weeks old, with a well developed root system). The older seedlings are more difficult to affect



Fig. 1—Radish seedlings. Note fluid level of control compared with that of dead plants immersed in bile extract solutions.

but the leaves are beginning to curl and at least one plant is dying."

In the following table are given the toxic effects of different bile extracts on tomato seedlings. Controls were run using only the nutrient solution.

Effect of Bile on Growth of Tomato Seedlings

Bile No.	Periods of Observation		
	3 hours	24 hours	72 hours
Controls in nutrient solution	grew normally		
77	Older leaves withered	Leaves dying	Shoots dead, most recent leaves still alive
93		Entire plant curling up dying	Dead
96	One leaf curled up and dead	1, 1, 1	Dead
98	One leaf bad condition	1, 1, 1	Leaves curled up but some of the smaller ones alive
99	Unchanged	Unchanged	Alive but apparently not growing
100	Older leaves drying up curling		Dead

It will be observed that in three hours the leaves of the seedlings showed a definite reaction to the presence of bile, they began to wither and curl. Only bile No. 99 failed to produce this change. The toxic effect of the bile was progressive and in twenty-four hours the leaves were plainly dying. At the end of seventy-two hours the seedlings in bile Nos. 93, 96 and 100 were definitely dead and those in bile Nos. 77 and 98 were in very bad condition. Only No. 99 resisted the action of the bile, and even this seedling failed to grow although it remained alive (Figs. 2 to 6).

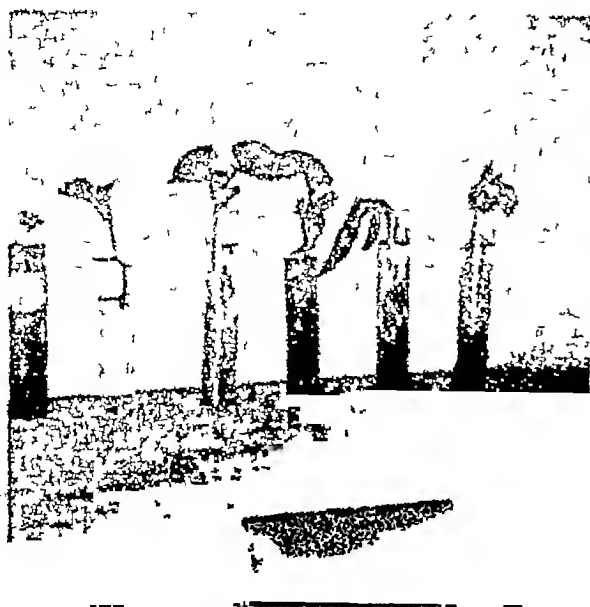


Fig. 2—Effect of various bile solutions on bean seedlings. The third plant from the left is the control. The others are immersed in solutions of the third portion biliary fraction.

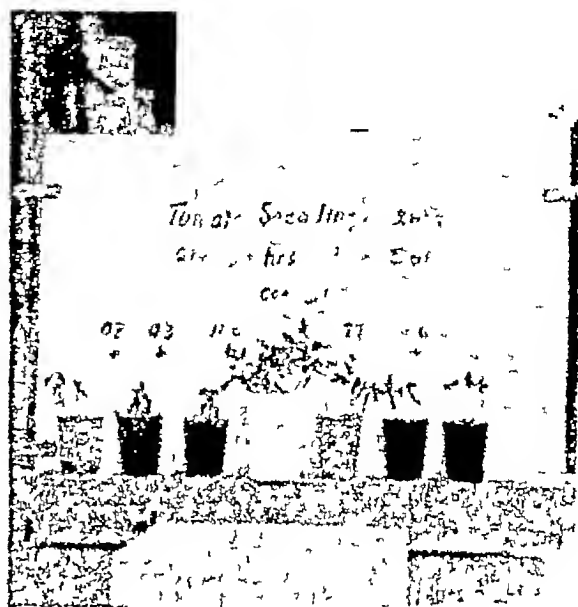


Fig. 4—Six two weeks old tomato seedlings after three hours' immersion in tumblers containing various solutions of bile taken from patients. The controls are in the center. Plants No. 93 and 100 are dead, for the others show deterioration.

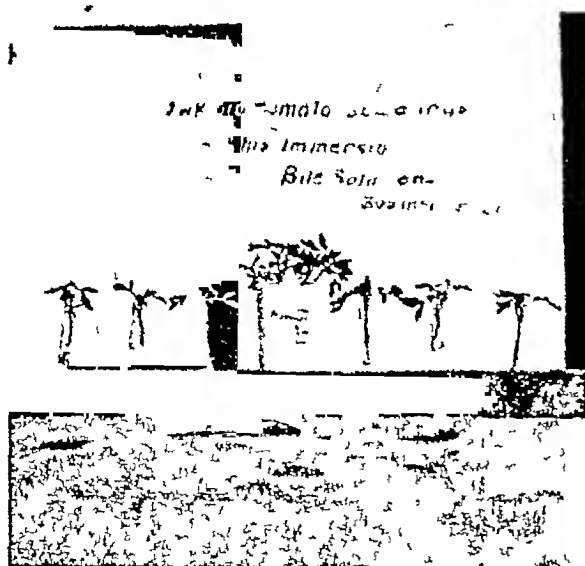


Fig. 3—Six tomato seedlings after three hours' immersion in bile solutions containing 300 mg of desiccated third portion biliary fraction showing varying degrees of toxic effect.

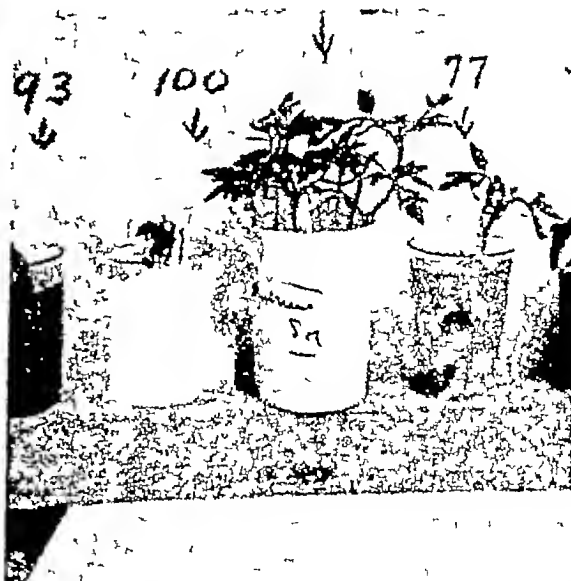


Fig. 5—A closer view of Fig. 4 showing the controls, the dead specimen No. 100, and the partially affected No. 77.

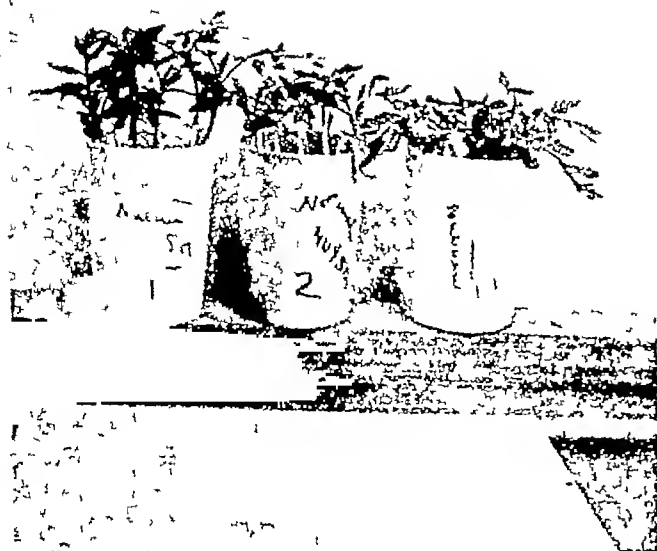


Fig 6—The early effects, on a larger number of plants, of immersion in bile solution. Container No 1 holds the normal controls, those in No 2 have been submitted for a short period to bile solutions, and in No 3 for a longer period. The plants in Nos 2 and 3 are noticeably wilted.

We tested Italian rye seedlings in nutrient solution and in that containing bile. These plants sprout on the surface and present a single long root with many lateral hairlike processes. After three hours the young root

hairs in the bile solution showed a tendency to agglutinate and lose their parallel arrangement (Fig 1). Measurement of the green stalks showed that the untreated seedlings were longer than those subjected to the action of bile extracts.

In both the animal and plant experiments the outstanding observation is that there is interference with respiration. That the consumption of water ceases altogether at a certain point was demonstrated in all our experiments with bile extracts on plant seedlings and there is, therefore, no reasonable doubt that this material contains a protoplasmic poison which affects plant life. There must, however, be some additional factor inasmuch as the bile salt solution was more promptly effective.

In the next experiment a few drops of each of the various bile extracts were injected by hypodermic syringe under the skin of a ripe grapefruit (Fig 7).



Fig 7—Bile solution injected under the skin of a ripe grapefruit. a After twenty-four hours a depressed area was observed at the site of injection, control points injected with distilled water developed no effect. b Section showing bile-injected area stained with cresol blue.

Rabbit No	Sex	Weight Kg	Injection Volume (mg)	Date	Date of Death	Remarks Fasted 24 hours
1	M	2.95	295	Nov 29		Bile salts
		2.816	563	Jan 23		" "
		2.85	855	Feb 13		" "
		2.685	939.7	Mar 7	Mar 8	Fasted 24 hours
2	F	2.54	254	Dec 5		Bile salts
		2.95	590	Jan 24		" "
		2.935	880.5	Feb 14	Feb 15	Fasted 24 hours
3	F	3.085	308.5	Dec 6		Bile salts
		3.27	654	Jan 30		" "
		3.35	1005	Mar 13		" "
		3.153	1103		Mar 14	Fasted 24 hours
4	F	1.82	182	Dec 12		Bile salts
		1.75	350	Jan 31		" "
		1.57	474	Feb 21		" "
		1.594	557	Mar 21		" "
5	F	2.46	246	Dec 13		Fasted 24 hours
6	F	2.44	244	Dec 22	Feb 1	Bile salts
		2.68	536	Feb 6	Feb 6	Fasted 24 hours
7	F	1.937	387.4	Feb 7		Bile salts
		1.988	594.6	Feb 27		" "
		2.044	715.4	Mar 21	Mar 22	" "
8	M	1.735	173.5	Nov 20	Nov 21	Fasted 24 hours
9	M	1.744	174.4	Nov 21	Nov 22	Bile salts
10	M	1.807	180.7	Nov 27	Nov 28	Fasted 24 hours
						Bile salts

After varying lengths of time depressions appeared at the sites of injection, and gradually deepened during the next forty-eight hours. Sections cut through these depressed portions revealed what seemed like areas of necrosis. Injections of the same amounts of distilled water in control guinea-pigs failed to produce any effect.

Bile salts injected into laboratory animals produced precisely the same results (10). In our studies the salts were found to be intensely irritating and led to local abscess formation. The following table is a short protocol on 10 rabbits to which bile salts were administered subcutaneously.

The doses of bile salts, initially 100 mg. per kilo-gram of body weight, were increased with each injection. In the first four animals, the heavier rabbits, it was possible to continue the dosage for several months, but in the last three, especially in rabbits 9 and 10 which were of the small pink variety, the initial dose killed within twenty-four hours. All rabbits finally developed tonic convulsions and it was suggested that death was due to amphiphaxis. In the older rabbits, and in those which had received repeated injections, diffuse renal and hepatic changes were found on microscopic examination. It is therefore apparent that these bile salts contained toxic substances capable of acting as protoplasmic poisons. It is interesting to note that the subcutaneous injection of bile salts produced intense irritation usually abscesses, although the solutions used were sterilized at 15 pounds pressure for twenty minutes. This same effect was observed by Lieber (11) working with Moon on dogs and caused them to use intravenous rather than subcutaneous injections.

Conclusion

1. There are present in the third portion (liver fraction) following duodenal drainage substances which are toxic to some animal and most vegetable life.

2. Whatever the nature of the toxic substances they occur in variable amounts in different specimens, some being relatively nontoxic, others definitely so.

3. We believe that duodenal drainage under satisfactory technical conditions removes a toxic factor which may explain some of the benefit resulting from this procedure in selected cases.

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Notes on Nutrition

The food conference at Hot Springs, Virginia, May 18 to June 3, 1943, referred back to the work done by the League of Nations in attempting to form agencies in all countries which would have government help in the work of nutritional surveys and food improvement. This conference was one of great importance even though it enjoyed a poor press and the public were not permitted to learn exactly what was accomplished. Referring to the work of the League on food consumption levels and the prevalence of malnutrition in various countries, it revealed that even in the U. S. A. about one third of the population suffer from malnutrition and that the one third of the selectees for the armed services who were rejected as physically unfit lived chiefly in the worst fed districts. At least 75 percent of the 1150 million inhabitants of Asia consumed diets far below health standards. Among India's 400 million, diseases of malnutrition are rampant and China, containing one-fifth of the human race has a chronic nutritional problem of greatest severity, made worse by the war. Keratomalacia, beriberi and osteomalacia are very common. Africa, Egypt and Mexico all show wide-spread effects of malnutrition. Indeed

the world as a whole shows a picture of world wide underconsumption of food. Poverty is given the credit for most of the world's malnutrition. The paradox of such suffering alongside of the bursting granaries with surplus food that cannot be sold was one of the reasons why statesmen have taken a keen interest in food. One of the reasons for the Hot Springs conference. The conference did not condone an economy of scarcity so far as food is concerned and felt that a civilization could not long endure who wilfully destroyed food. They felt that enough food could be produced to feed the world because of modern knowledge of production, but that this goal could not be achieved under wartime conditions. Each nation must see that it has enough food for its own people, but this requires international teamwork. A new world-wide economy based on a better consumer purchasing power seemed obviously necessary and this depended upon conservative statesmanship after the war.

The conference resolved to set up at once an Interim Committee to make plans for a permanent international organization in food and agriculture and to advise all governments participating of the obligations to be as-

sumed. By utilizing existent food agencies, the Commission probably will eventually form a world-wide network for the technical training, research and exchange of information. The government of nations not represented at the conference (neutrals and enemy) must also be brought into the permanent organization. This organization will represent the various governments and will be able to provide exchange of services when needed. If the organization is given the power to make suggestions respecting nutrition, agricultural products and problems of agricultural population and farm labor it would exert a powerful influence in economic and social affairs throughout the whole world. "The Interim Commission must also consider the desirability of assigning to the permanent organization functions in the field of development of agricultural resources and orientation of production, agricultural commodity arrangements, agricultural cooperative movements and land tenure." In Europe certain areas would need to increase milk production and decrease grain production. Producer and consumer cooperative societies might be encouraged to lower production costs, and legal barriers to the same would be investigated by the permanent organization. The conference urged all governments to start at once on statistical studies aimed at improving conditions of malnutrition within their nations so as to raise general standards and protect the vulnerable groups,—pregnant and nursing mothers, children, workers, low income groups and those with large families. The dietary allowances of the Food and Nutrition Board of the National Research Council was favorably held up as an example of a modern standard which has had wide acceptance. A national nutrition organization without administrative powers will need to be set up in the U. S. A., and the government will need to review legislation on health, agriculture and nutrition so that suitable policies may be carried out. A vigorous campaign must be started against our chief deficiency diseases,—pellagra first of all. Since our own government convened the conference, it is up to us to implement its suggestions. Great Britain and the U. S. A., through responsible Statesmen have already indicated their acceptance of the recommendations of the Conference. The national administration will be well served if it can count on an enlightened public opinion to support the social and economic measures which are necessary in the U. S. A. to increase our food resources and improve the diets of all our people. The aims of the conference were not political in flavor and dealt with subjects of basic importance to mankind.

Specificity of the ariboflavinosis syndrome in man
Cheilosis, a vascularizing keratitis and the magenta tongue with flattened papillae regarded as signs of ariboflavinosis, may occur in other diseases as well although these lesions in food deficient patients often do respond to the administration of riboflavin. Perhaps these lesions occur in persons with riboflavin deficiency but are really caused by deficiencies in unidentified members of the B-complex. Many cases respond, not to riboflavin but to B-complex. Seborrheic dermatitis also falls into this category. Certainly these signs can

occur separately or in combination in persons with riboflavin deficiency, whatever be their cause (Proc Soc Exp Biol Med 43, 660, 1940) (Am J Med Sci 205, 214 1943)

Vitamin concentrates in war and postwar diets
Allied nations will be in a better position to deal with post war nutrition problems this time than in 1918 because of better knowledge. Vitamin concentrates may be used when given by an experienced physician. They should be available in good supply because epidemics of vitamin deficiency are bound to occur within two years after the cessation of war. But as a practical method of preventing such diseases the concentrates are of less practical value than diets of high protein content, which may be regarded in general as good diets of natural foods. Stores of wheat skin, milk powder, dehydrated butter, dried meat and fish should be ready for post war food relief. In Spain in spite of very poor diets during the war scurvy was rare and famine edema did not occur for nearly two years, though eventually beriberi and pellagra became endemic. In war time, pregnant women and children require special care and here the use of vitamin concentrates is of value. In Britain the consumption of potatoes and whole wheat bread probably will render supplementation with B-complex unnecessary. The British school children need extra ascorbic acid. War workers and members of the armed forces need optimal amounts of vitamins, and research has cast doubt on the need of supplementing the army ration with vitamins. Probably vitamin A and carotene do no good in increasing night vision except in individuals previously deficient in this element. A survey of scientific opinion leaves the general impression that vitamin concentrates have their value in treating deficiencies known to exist but that it is unnecessary to supplement diets which are known to be adequate.

Fat absorption in sprue and jejunoileitis
The fact that the normal post-prandial rise in blood fat and serum vitamin A does not occur in sprue but does occur in cases suffering from jejunoileitis suggests that in sprue there may be some fault of small bowel absorption one which is seemingly overcome by the administration of liver extract. More work is needed on this subject (Gastroenterology 357, 1943).

Urea as partial protein replacement for ruminants
Information from many scientific sources confirm the fact that urea may be used along with a low protein diet in ruminants with good results as judged by growth, reproduction and milk production. The urea fed to the animal is synthesized into amino acids and proteins in the fourth stomach by enzymatic activity of certain bacteria, which need a substrate high in carbohydrate. Such animals are kept in nitrogen balance in spite of their low protein ration. Urea should be about 1 to 3 percent of the ruminant's dry ration.

Vitamin C deficiency in relation to bone and muscle injury
It might be well to give vitamin C supplements to patients with healing fractures since recent work indicates that experimentally in guinea pigs a lack of Vitamin C causes hyperostosis (laving down of periosteal bone) with some tendency to ankylosis of

joints as well as swelling of muscles with overgrowth of connective tissue (Nature 151, 395, 1943)

Pituitary cysts in vitamin A deficient cattle The development of cysts in the pituitary glands of cattle deficient in vitamin A is now a well recognized phenomenon, though such cysts are extremely rare in normal cows. Thus far such cysts have not been observed to form in other animals deprived of Vitamin A (J. Nutrition, 24, 15, 1942)

Human requirements of riboflavin Probably the correct daily requirement of riboflavin is 0.5 mg per 1000 calories. In extensive experiments recently carried out on inmates of a State Hospital, even those most restricted on this food factor failed to show any clinical evidence of ariboflavinosis. This may have been because they had good stores of the vitamin previous to the experiment. We need experiments which will produce actual lesions so that we can know for sure what signs if any represent this deficiency (J. Nutrition, 25, 361, 1943)

Massive doses of vitamin D in the prevention of rickets It is certain that no matter how well it works, the technique of giving occasional massive doses of vitamin D to infants is unnecessary and the best evidence of this is the fact that the investigator had difficulty finding any cases of rickets. The use of sunlight irradiated milk or cod liver oil by modern American mothers has practically obliterated the disease, and medical schools today have trouble finding cases for teaching. The fact, however, that the massive dose method works, is evidence of the body's power to store this food factor over long periods of time. (J. Pediatrics 22, 396, 1943)

Feeding quickly moving troops The new field ration K is contained in 3 boxes, one for each meal of the day. Each box is 6 inches long, 4 inches wide and 2 inches deep, and is impervious to water, chemical warfare agents and vermin. The day's supply consists of canned ham and egg, canned meat or fish, 2 types of biscuit, a fruit bar, a chocolate bar, a beverage (soluble coffee), bouillon powder, lemon powder, malted milk-dextrose tablets, sugar, chewing gum and cigarettes. It provides per day 3400 calories, 115 gms protein, 22 mg iron, 1000 mg calcium, 2000 mg phosphorus, 3 mg thiamin, 25 mg riboflavin, 25 mg nicotinic acid, and 55 mg ascorbic acid. This ration is acceptable to the soldier for a longer period of time than any other rations yet devised for a similar purpose.

Vitamin and mineral retention in cooking vegetables Vegetables should be cooked in as little water as possible in order to conserve vitamins and minerals. This was proven by cooking experiments, using various types of vegetables in the one case cooking in little water, in the other using much water. The vitamin and mineral content being determined before and after cooking. It was found that significant savings were obtained by the new method of cooking (Food Research 8, 115, 1943)

Poorly absorbed sulfone drugs and deficiency disease It is now pretty well established that such poorly absorbed drugs as sulaguanidine and succinyl sulfathiazole produce effects in the intestine of animals

which tend to stop growth. They kill or alter the B. Coh organisms which normally have a fermentative faculty in the production of biotin and folic acid. Even vitamin K may be produced in the human bowel in sufficient amounts by the action of this organism. Hemorrhagic disease may be found as a result of the prolonged ingestion of these sulfones where a purified diet is used. Anemia and leucopenia may occur. Experiments with animals on purified diets showed that these blood changes are much more common when sulfathiazole and sulfadiazine are used than in the case of sulfanilamide. The use of liver extract or whole dried brewers yeast promptly improved the blood picture in these cases.

Supplementary food and the nutrition of school children It is probably not worth while in America at least to adopt the method of condensing the daily amounts of vitamins and minerals into one daily article of diet such as a special soup, because an experiment with school children certainly showed little improvement except in better iron levels in the blood and better concentrations of vitamin C, and these could have been obtained by the use of simple iron and vitamin C supplementation (J. Am. Diet. Assn. 19, 182, 1943)

Amino acids and plasma proteins It has been shown that nitrogen balance can be maintained and the formation of plasma proteins can be stimulated by the administration of mixtures of amino acids orally or intravenously. There are ten amino acids particularly which are vital in this connection, the omission of one or more causing poorer results to be obtained. It has been shown that the amino acids are incorporated into new plasma protein. Plasma protein is considered to be in dynamic equilibrium with proteins of other tissues. Plasma proteins can contribute to the building of hemoglobin or, when necessary, hemoglobin can contribute to the formation of plasma proteins (J. Exp. Med. 77, 375, 1943) (Ibid 77, 277, 1943)

Effects of vitamin A depletion in man On a vitamin A deficient diet, man shows an early and severe reduction in his blood carotene but the blood levels of vitamin A remained unchanged for many months on an intake of only about 75 USP units daily. In infants of 3 months of age, depletion rapidly occurs because infants have less vitamin A stored. The occurrence of fever interferes with the mechanism by which vit. A is released from the liver and a temporary fall in blood vitamin occurs, only to return to normal when the fever has gone (Arch. Int. Med. 71, 474, 1943)

Vitamin requirements of animal strains A newly recognized factor which promises at times to complicate results of feeding experiments is the variation in vitamin requirements even among different strains of a given species. This has been found true for thiamine in chicks and white rats, for choline in white rats, and for riboflavin in chicks. It is of interest that the variation in vitamin requirements is an inherited characteristic and males seem to require more than females (J. Agr. Research 58, 307, 1939) (Science 87, 90, 1938) (Proc. Soc. Exp. Biol. Med. 52, 281, 1943)

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The Treatment of Dysentery Carriers With Succinylsulfathiazole: Observations On The Minimal Effective Dose

By

PAUL S BARKER, M D

ANN ARBOR, MICH

THE purpose of this paper is to report observations bearing on the minimal effective dose of succinylsulfathiazole in the treatment of carriers of dysentery bacilli¹

Succinylsulfathiazole has been found effective in the treatment of dysentery carriers and of patients with acute bacillary dysentery Kirby and Rantz (1) administered orally 0.25 Gm of the drug per kilogram of body weight daily, divided into four equal doses, to five dysentery carriers The duration of the administration of the drug varied from five to fourteen days The stool cultures of all five patients were negative for dysentery bacilli within one week after treatment was begun and remained negative during the follow-up period of thirty to sixty days

Poth, Chenoweth and Knotts (2) reported the prompt recovery of all of twenty patients with bacillary dysentery following the oral administration of succinylsulfathiazole in amounts of 0.25 to 1.0 Gm per kilogram daily, divided into six equal portions and given for two to seventeen days They observed that the response to the drug was almost immediate even when the disease had been present for as long as three months before treatment was begun They also found that the patients who received smaller doses responded better than those who received larger doses They felt that in many instances unnecessarily large amounts of the drug were given for longer periods than required They discussed the prophylactic use of the drug and stated "Since the minimum effective therapeutic dose of succinylsulfathiazole has obviously not been established, a satisfactory prophylactic dose might be surprisingly small" Support for this optimistic suggestion is found in the successful prophylactic use by Scott (3) of sulfaguanidine in doses of 0.5 Gm three times daily by mouth

Smyth and his associates (4) found the daily administration of 0.15 Gm per kilogram inadequate A patient with acute bacillary dysentery was given this amount of the drug initially and a similar amount daily for four days Throughout the period of treatment and for the next sixteen days eleven stool cultures were negative for dysentery bacilli Then on six consecutive days the stool cultures were positive for these organisms A second course of succinylsulfathiazole was given, using 0.5 Gm per kilogram as the initial dose and the same amount daily for four days Stool cultures became negative after one day of this treatment and re-

mained negative throughout twenty-three days of observation

In the routine examination of hospital food handlers, five individuals were found to have dysentery bacilli in their stool cultures All were given physical examinations and appeared to be in good health although one (Case 2) had experienced a bout of diarrhea two weeks prior to the starting of treatment and another (Case 5) had mild hypertension The patients were ambulatory Their diets were not modified

The first three patients were given 3 Gm of succinylsulfathiazole four times daily, 12 Gm per day, for seven days This treatment did not eliminate the dysentery organisms from the stools A second course was then given, using the same amounts of succinylsulfathiazole for fourteen successive days Following this repeated stool cultures in all three patients were negative for dysentery bacilli during the period of observation which varied from 34 to 131 days The daily doses of succinylsulfathiazole were 0.147, 0.195, and 0.220 Gm per kilogram of body weight for these three patients

The fourth patient was given 3 Gm of succinylsulfathiazole four times daily, 12 Gm per day, for fourteen days The stool cultures continued positive for dysentery bacilli A second course of the drug was then given, using a dose of 4.5 Gm four times daily, 18 Gm per day for five days Thereafter, stool cultures were consistently negative for dysentery bacilli for a period of twenty-five days after the larger dose was started In this case, a dose of 0.166 Gm per kilogram for fourteen days was ineffective, while 0.25 Gm per kilogram for five days successfully eliminated the dysentery organisms from the stools

The spontaneous disappearance of dysentery bacilli from the stools of carriers may introduce a source of error in observations such as these This is illustrated by the fifth patient who had two positive stool cultures A third specimen of stool was obtained for culture and it was negative for dysentery organisms Without waiting for the report of the third stool culture, however, the patient was started on a course of succinylsulfathiazole, 3 Gm four times daily, 12 Gm or 0.154 Gm per kilogram daily, for one week Thereafter, three successive stool cultures were likewise negative for dysentery bacilli over a period of twenty-three days after treatment was started

Only one patient reported any unfavorable effects of the drug This patient (Case 3) had four or five loose stools daily while taking 12 Gm 0.220 Gm per kilogram, daily for fourteen days

From the Department of Internal Medicine, University of Michigan Medical School, and the University of Michigan Hospital
Submitted Sept. 24 1943

The pertinent data are shown in the accompanying table. It should be noted that in all cases the stool cultures were negative for several days after the initial, ineffective course of treatment, but subsequently became positive. This illustrates the importance of obtaining repeated stool cultures for at least three weeks after the termination of therapy, a point which has been emphasized by Smyth and his associates (4).

It is realized that the number of patients observed is small and that further studies are desirable. These observations suggest, however, that relatively small doses of succinylsulfathiazole will eliminate dysentery bacilli from the stools of most carriers if administered over a long period of time. From the practical standpoint, however, it would seem better to give the drug in amounts sufficient to eliminate the organisms in a short time and with certainty. It is probable that 0.25 Gm per kilogram daily, in divided doses, for five to seven days, is the smallest amount of succinylsulfathiazole which will uniformly eliminate dysentery bacilli from the stools of carriers in a short time.

SUMMARY

Succinylsulfathiazole was given to three dysentery carriers in amounts of 0.147, 0.195 and 0.220 Gm per kilogram of body weight daily. These amounts did not successfully eliminate the organisms from the stools when given for seven days, but when given for fourteen

days effectively eliminated the dysentery bacilli from the stools. A fourth patient did not respond to 0.166 Gm of the drug per kilogram daily for fourteen days, but was rendered free from dysentery bacilli by 0.25 Gm per kilogram daily for five days. A fifth patient recovered spontaneously from the carrier state.

Although relatively small amounts of succinylsulfathiazole are effective if continued for a long time, it would seem more practical to give at least 0.25 Gm per kilogram daily for five to seven days, an amount which should uniformly eliminate dysentery bacilli from the stools of carriers in a short time.

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Days	Case 1 81.8 Kg	Case 2 61.4 Kg	Case 3 54.5 Kg	—	Case 4 72 Kg.	Case 5 77.7 Kg
	+ (112 days)					
70		+				
63			+			
56		0.195 Gm./Kg for 7 days	+		+	
49	+					
42		—	+		+	
		—			0.166 Gm./Kg for 14 days	+
35	+	+				
	0.147 Gm./Kg for 7 days					
28	—		0.220 Gm./Kg for 7 days			+
21					—	
14	+		—		+	
7	+	+	+			—
0						
7	0.147 Gm./Kg for 14 days	0.195 Gm./Kg for 14 days	0.220 Gm./Kg for 14 days		0.25 Gm./Kg for 5 days	0.154 Gm./Kg for 7 days
14	—	—	—		—	—
21	—	—	—		—	—
28	—	—	—		—	—
35		—	—			
42		—				
		—				
49	— (131 days)	— (96 days)				

The treatment of dysentery carriers with succinylsulfathiazole. The daily dosages of the drug are shown. The zero day is in each case the day on which the effective course of treatment was started. The plus signs indicate positive and the minus signs negative stool cultures. The first two cultures in Cases 1 and 5 were positive for *B. paratyphosus* flexneri. All other positive cultures showed *Shigella* *alkalescens*.

Gall Bladder Functions after Sub-Total Gastrectomy: Clinical and Roentgenological Observations

By

I R JANKELSON, M.D.

and

S A ROBINS, M.D.

BOSTON, MASS

IT IS well known, that gall bladder disease may cause not only secretory and motor disturbances of the stomach but also gross changes in the gastric mucosa. On the other hand, what effect disease of stomach has upon the gall bladder is not sufficiently investigated.

From the literature we have culled the following data. Morgan, Crandall and Ivy (1) have produced in five dogs a pouch of the entire stomach. After the gall bladder was visualized roentgenologically with the sodium salts of tetraiodophenolphthalein the stomach was lavaged for two or three hours with egg yolk. In two dogs the gall bladder was found to be empty in two hours. In three dogs no emptying occurred. The same authors (2) showed in five dogs with pouches of the entire stomach and an esophageoduodenal anastomosis that the gall bladders filled normally with the intravenously administered dye. In four experiments egg yolk was then given by mouth. Evacuation of the gall bladder was prompt in three instances and delayed in the fourth.

Boyden and Berman (3) believe that the gall bladder empties significantly faster in patients with gastric and duodenal ulcers, probably due to hypermotility of the stomach and not to hyperacidity. On the other hand, Feldman (4) showed sluggish or non-contracting gall bladders in the presence of peptic ulcer in 27.3 per cent of cases studied. According to Leb (5) who studied 100 duodenal ulcer patients by intravenous cholecystography, 26 per cent of organically healthy gall bladders failed to fill. Robins and Goldberg (6) state that in a large percentage of duodenal ulcer cases no gall bladder shadow is visible when the dye is given by mouth. Feldman (4) obtained satisfactory gall bladder shadows in 87.7 per cent of patients with peptic ulcers when larger doses of dye were given by mouth. According to him the density of the gall bladder shadow is often markedly reduced in the presence of a peptic ulcer and with small doses of the dye the gall bladder may show no filling.

Ritchie and Boyden (7) believe, that carcinoma of the stomach has no demonstrable effect on the filling of the gall bladder with the intravenously administered dye, nor does the carcinoma of the stomach affect the rate of emptying of the gall bladder. Our own experience like that of many others is that in the presence of a pyloric stenosis, the gall bladder may fail to fill in the

usual manner when the dye is given by mouth. When filled, under such circumstances, the gall bladder may fail to empty normally after a fat meal.

According to Ritchie and Boyden (7) in the presence of a gastroenterostomy the gall bladder probably empties faster than normally. On the other hand, Kalk and Nissen (8) showed that in the presence of a functioning gastroenterostomy one in twelve gall bladders did not empty in the usual manner after a fat meal. They suggest that the failure of the gall bladder to empty occurs only in the first few months post-operatively.

We could not find any reports about cholecystographic studies after a partial gastrectomy for either peptic ulcer or gastric carcinoma. In our clinical work we have observed four cases of cholelithiasis in patients who have had a partial gastrectomy and in whom no evidence of gall bladder disease was found either pre-operatively or on abdominal exploration during the operation. These cases are briefly reported.

CHOLECYSTOGRAPHIC INVESTIGATIONS

In order to elucidate the effect of partial gastrectomy upon the functions of the gall bladder we have investigated 15 cases. All patients have had partial gastrectomy for either a peptic ulcer or gastric carcinoma. None of the patients had signs or symptoms suggestive of gall bladder disease either before or after the operation. In none of the patients was there any gross evidence of gall bladder disease during the abdominal exploration accompanying the gastric resection. In the interval between the partial gastrectomy and our investigation which varied from a few months to four years, there were neither serious infections nor metabolic disturbances which are likely to initiate gall bladder pathology.

Our studies are divided into two phases. First the filling of the gall bladder after the administration of the dye by the intravenous or oral route and second, the effect of partial gastrectomy on the normal emptying of the gall bladder.

FILLING OF THE GALL BLADDER

In order to determine whether the gall bladder fills in the usual manner in the presence of altered mechanics as a result of partial gastrectomy, we have observed 15 patients who have had a partial gastrectomy. In all cases the gastric secretion was either markedly diminished or free HCl was absent before and after histamine

stimulation. In 10 cases, the dye was given intravenously in the usual manner, while in 5 cases, 8 gms of dye was given by mouth and plates were taken after fasting 14 hours. In all but one case in which the dye was given intravenously, the gall bladder filled in the usual manner. The density of the gall bladder shadow was greater when the dye was given by vein than when administered by mouth. No demonstrable stones were present in any of these cases.

The interval between the partial gastrectomy and the performance of the test was of no consequence. The size of the gall bladder apparently was not affected by the preceding operation, since in our series there were rather large but not necessarily enlarged gall bladders, as well as small ones. Hence, we must conclude that a previous subtotal gastrectomy may affect the normal filling of the gall bladder in about six per cent of the cases.

EMPTYING OF THE GALL BLADDER

After the gall bladder was filled with tetraiodophenolphthalein, a standard fat protein meal was given each patient and the concentration of the gall bladder shadow as well as the emptying of the gall bladder observed within a half hour. All but two contracted the gall bladder and concentrated the dye within the organ in the usual manner. In 2 cases (14%) the concentration and evacuation of the dye was definitely delayed. This occurred independently of the interval between the partial gastrectomy and the test and apparently was not related to the gastric secretions or gastric motility. Hence we must conclude that in some cases a partial gastrectomy may result in motor and concentration dysfunction of the gall bladder.

DISCUSSION

This evidence probably explains our clinical observations, that following a subtotal gastrectomy disturbances of the gall bladder may occur. The changes appear to be at first motor disturbances of the gall bladder, later probably biliary stasis and eventually gall stone formation with or without infection of the gall bladder walls. Thus, in approximately 20 per cent of patients with a partial gastrectomy, a tendency to gall bladder disturbance can be observed, a complication which to the best of our knowledge has not been heretofore considered.

The mechanism of this biliary dyskinesia is most likely humoral (cholecystokinin) inactivity. This is due in part to diminished or absent HCl in the stomach, which is the normal activator of this hormone, in part to changes in the duodenal mucosa as a result of relative inactivity of this portion of the intestinal tract. Other factors, probably of lesser importance also play a part in the causation of this disturbed motor function of the gall bladder. Among these contributory factors one should mention diminished peristalsis within the duodenum and thus a lessened 'milking action' and lack of normal distention in the duodenum. Apparently in most cases other factors such as elastic recoil of the gall bladder, the secretory pressure of the liver and the nervous control together with a lessened humoral excitation are sufficient to properly empty the

gall bladder, thus preventing stasis and eventually infection and gall stone formation. However because of these changes in the evacuation of the gall bladder, a predisposition to gall bladder disease may develop in patients who have had a partial gastrectomy.

CASE REPORTS

Case I M H, male, age 56, was admitted to the hospital in November, 1938 with a diagnosis of gastric carcinoma. The diagnosis was made on roentgen ray and gastroscopic evidence. In 1933, a mild diabetes was discovered. On a restricted diet without insulin he showed glycosuria only occasionally. In 1936, a diagnosis of prepyloric ulcer was made on a roentgen ray examination. Two Graham tests revealed no demonstrable disease of the gall bladder.

At operation a carcinoma of the pyloric end of the stomach was found, also involvement of the regional glands. Exploration of the abdomen revealed no liver metastasis and a normal gall bladder. A subtotal gastrectomy was performed. The patient made an uneventful recovery.

In May, 1939, a check up examination of the gastrointestinal tract revealed no evidence of recurrence of the cancer. The gastro-jejunostomy functioned well.

In December, 1939, the patient developed painless jaundice, at first attributed to either pressure from enlarged carcinomatous glands on the common bile duct or intrahepatic metastasis. However, within eight days the jaundice disappeared and the stools became normal in color.

In January, 1941 the patient had a typical gall stone colic followed in eighteen hours by deep jaundice and later by clay colored stools. Vis ble jaundice cleared in 9 days. The patient refused further roentgen ray investigation.

Case II (Courtesy Dr Wekstein) B W, male, had in 1928 at the age of 29 a pyloric resection and a gastro-enterostomy for a duodenal ulcer. Because of recurrent bouts of hemorrhage and persistent pain he had in August, 1932, a subtotal gastrectomy, at which time a gastro-jejunal ulcer was found. Exploration of the abdomen revealed a normal gall bladder. Following this operation the patient was relatively symptom free on a rigid diet till December, 1937, when he passed again a tarry stool. His R B C was 2 300 000 and Hg 60%. Gastric analysis showed free HCl. Under medical treatment he made an uneventful recovery. In January, 1938, he had a sudden attack of severe sharp epigastric pain which radiated to the right upper quadrant. Three weeks later he had a similar attack associated with vomiting. On examination he showed some voluntary spasm in the right upper quadrant and localized pain beneath the anterior costal margin. Temperature was 104. W B C was 33 900. Icteric index, 15. Three days later a cholecystogram by the intravenous method showed a poorly functioning gall bladder. Four days later a cholecystectomy was performed. The pathologic report was acute and chronic cholecystitis and cholelithiasis. He made an uneventful recovery.

Case III R Z, female, age 37, had in 1933 a partial

gastrectomy for a duodenal ulcer which remained active despite several hospital admissions and a previous pyloroplasty. Neither before the operation, nor at either of the two operations was there any evidence of gall bladder disease.

Following this operation the digestive symptoms persisted. On several occasions the question of a marginal ulcer was raised, but never proven. Repeated gastroscopies showed post-operative gastritis and on one occasion a small superficial ulcer near the stoma. There was also a definite neurosis which colored the clinical picture. She was treated symptomatically but remained a semi-invalid. In 1939, a Graham test revealed multiple stones within the gall bladder. Cholecystectomy was performed, again without complete relief of the patient's symptoms.

Case II G. S., (Private Case) female, age 54. In 1938, the patient had a subtotal gastrectomy for repeated exsanguinating hemorrhages. At operation a duodenal ulcer was found. The gall bladder appeared normal, bile could be expressed and there were no palpable stones. When first seen in May 1940 the patient again passed a tarry stool. The RBC was 3,500,000 Hg 60%. The stools showed occult blood for seven days thereafter they remained free of occult blood. A complete gastro-intestinal roentgen ray examination revealed a partially resected stomach with a well functioning stoma. No ulcer was demonstrated. The gall bladder filled poorly and appeared somewhat mottled. In June 1941, this patient had a typical gall stone colic without jaundice. A repeat Graham test showed definite faceted stones within the gall bladder. Further surgery was refused by the patient.

CONCLUSIONS

Following a subtotal gastrectomy, the gall bladder functions may be interfered with. In our studies the gall bladder failed to fill in 6 per cent of the cases and the emptying was delayed in 14 per cent. The latter may lead to stasis within the gall bladder, later infection or gall stone formation. Four patients who developed gall stones after a subtotal gastrectomy are reported.

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Early Experimental Fistulas of the Stomach

By

M. H. F. FRIEDMAN,* Ph.D.

PHILADELPHIA, PA.

THIS year is the one-hundredth anniversary of the publication of "Traite analytique de la digestion" by N. Blondlot (1). For more than fifty years this work was to influence the ideas and experiments on digestion of physiologists and chemists throughout Europe. The appearance of this book in 1843 also marks an important event in experimental surgery—the production of a chronic gastric fistula.

Although fistulous conditions of the stomach were known and described long before Blondlot's time, these occurred in man and animals usually only as the result of accident or pathological processes. There were numerous predecessors to Alexis St. Martin but no predecessor to William Beaumont who realized as he did the value of the condition as a means of studying digestive processes and who took full advantage of it. The first to establish a gastric fistula with the intended purpose of studying the physiology of the stomach were Bassov

in Russia and Blondlot in France. Each worked independently of the other and at about the same time. Bassov's work was published in 1842 (2) and Blondlot's in 1843. Both men were deeply influenced by Beaumont's work which was published about ten years earlier (3) and both attempted to duplicate by surgery on the dog what accident had performed in St. Martin. According to Pavlov (4), this marked the starting point of the modern methods for obtaining gastric juice.

The need for a method of obtaining pure gastric juice was felt keenly by Blondlot. He wrote:

"If, in spite of the numerous works on digestion, we do not know much about the gastric juice, it is above all due to the difficult procedure employed in obtaining this fluid. Our ideas about this digestive agent *par excellence* are vague, incomplete, and often contradictory. Almost all procedures for obtaining the juice furnish an impure product which is so scanty in quantity that analysis is difficult.

*Department of Physiology, Jefferson Medical College, Philadelphia.
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"The means employed until the present for obtaining gastric juice are (1) killing an animal some time after he has eaten, (2) introducing into the stomach a dry compressed sponge to which is attached a string to enable it to be withdrawn later, (3) utilizing the faculty possessed by some people of vomiting at will, and (4) finally profiting by cases of gastric fistulas which are established spontaneously in man following accidents. As can be readily seen, all these procedures are far from offering an equally satisfactory result."

Blondlot discussed these procedures in detail and pointed out the advantages and disadvantages of each. His description of the technique he employed to make a fistula of the stomach makes interesting reading. It must be borne in mind that at this time anesthesia and aseptic surgery were unknown.

"This procedure suggested itself to me from the preceding one (the case of St. Martin) of which it is only an imitation. I asked myself if it would not be possible to produce artificially in animals gastric fistulas which resemble those that sometimes develop in man after certain accidents. This seemed to me fairly easy to do since there are recorded cases of gastrostomy performed successfully in man, in whom vivisection is always much more dangerous than in animals."

"To execute this experiment I chose a young dog of great size, one not yet fully grown but well behaved. About one-half hour before the operation I fed him a modest meal of meat and bread. With assistants holding the animal I made an incision from the xiphoid process down towards the pubis for a distance of seven or eight centimeters. The peritoneum was cut with care so as not to injure the intestine. The stomach was easily recognized since it was moderately distended with food. The stomach was pulled towards the incision and cut with the point of a knife. I then passed a silver string through the stomach at two points, so that the stomach enclosed between the two sutures was three to four centimeters and lay towards the cardiac extremity of the greater curvature. With assistants holding the two ends of the string, I proceeded to close the wound after first replacing into the abdomen the intestines which had escaped from it. Several sutures were sufficient. Both ends of the metal strings protruded to the outside and were wrapped about a piece of wood in such a manner as to bring the portion of the stomach enclosed by the string in contact with the inner surface of the wound. Needless to say, this caused the stomach to fit against the abdominal wall so that a fistula was established."

"During the operation the dog vomited some of its food. He later ate what he had vomited but refused all other food. I gave him some milk on the second day which he drank with pleasure. By the

third day he played and ran about just as though he had not had a wound."

"On the week following I tightened the silver ligature daily by twisting it around the wood until, on the 17th day, it came away completely from the stomach. I could now introduce into the stomach a narrow sound through which flowed out various liquids that were fed the animals, this assured me that the instrument really was in the gastric cavity. To enlarge the wound I introduced several fragments of dry sponge which closed the opening and at the same time hindered the escape of food."

"Fifteen days after the first experiment I repeated it on another dog with the same success. I kept both animals in a state of perfect health for three months during which time I used their fistulas not only to obtain gastric juice in abundance but also to carry out experiments on digestion within the stomach. The second dog was sacrificed for a certain purpose. As for the first, he is today still with me and although for two years I have utilized his fistula to collect gastric juice and chyme or to introduce sounds, tubes, thermometers, etc. into the stomach, he is still in good health and is fat, active, alert and enjoys an excellent appetite."

In addition to establishing a gastric fistula, Blondlot was apparently the first to use a metal gastric cannula. He was bothered by the extreme rapidity with which the fistula tended to close. To overcome this he dilated the wound and introduced a flanged silver cannula so that, as he expressed it, "it was fixed in the wound like a boutonniere in a buttonhole."

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ERRATUM

In the comment of Dr. Alice R. Bernheim's article "For Better Nutrition," which appeared in the November issue of this Journal, it stated that "Nowadays, infants are fed every few hours from the very beginning of their lives," whereas it should have read "Nowadays, infants are fed every four hours from the very beginning of their lives."

Editorial

DO YOU AGREE?

Two things on the part of a doctor destroy morale in the patient,—rubber heels and whispering in the sick room

Do not hand a diet list to an accomplished gourmand unless you wish to make him sick

If you think you have the diagnosis but are not quite sure, just put "pseudo" in front of it, and you will probably be correct.

Vomiting in a person who never vomits usually means organic disease, but in nervous people it often is induced by tickling the palate

Belching which gives comfort is not complained of, but air swallowers make a big story to call attention to their habit

A bitter taste in the mouth is a sign of a nervous individual but a salty taste (without blood) means fatigue.

A bad breath seldom facilitates diagnosis, but there is a smell of malignancy in the gastric contents of persons with cancer of the stomach

Play down focal infection to some extent, but do not overlook a dead or abscessed tooth

Fastidious persons call themselves constipated when the daily stools are a little small because they judge the efficiency of their excretory function by the sensation of sphincteric dilatation

Some people use the word "indigestion" when they mean constipation

Many persons have used rather drastic purgatives all their lives without developing symptoms of indigestion

A few persons otherwise mentally normal claim that their bowels never move

Persons who usually have three evacuations daily think they are constipated if they have only two

Persons whose bowels move only once a week seldom complain of constipation

Diarrheas which last for years are harmless and are due to intestinal hurry, the colon not having time to absorb much water from the food mass

The patient who is utterly unable to describe how he feels, feels very badly

A woman who smiles as she describes her pain is always hysterical.

A carefully taken history is of greater value in diagnosing peptic ulcer than a careless fluoroscopic examination

Appendicitis can be diagnosed only by the man who has his hand on the abdomen while the pain is there

In very chronic pain in the right lower quadrant of the abdomen, the appendix seldom is responsible

The commonest cause of abdominal distress is constipation

The most serious cases are those with the briefest complaints

The less you find wrong with a patient, the longer must be your explanation of his symptoms

The hypersensitive patient has a moist eye, and he lowers his brows when you raise your voice

The commonest cause of abdominal rigidity is ticklishness

The terminal stage of cardio-vascular-renal disease without edema shows as rapid weight loss as cancer

Ptyorrhea seldom causes a symptom-producing gastritis

Many physicians still get good results from long prescriptions

One sometimes meets a patient who does not need a sedative

The patient who boasts of his health may merely be depressed

The woman who cannot make a single decision becomes a difficult patient

Looking at the patient's tongue has come back into vogue, but you have to be good to get away with it

Today the scale salts often give more dramatic results than the vitamins

Many a man thinks his xiphoid process is a tumor

The first interview will tell you whose medical column the patient reads

There is no greater builder of confidence than an admission of ignorance

A physician gets closest to his patient on the day he himself feels ill

The older a doctor gets, the less he tells his patients
Intestinal obstruction in August is likely to be due to eating corn

Renal stone is the only disease that makes patients turn somersaults in bed

The commonest causes of worry are fear of illness and lack of money

Some of the healthiest individuals eat the most monotonous diets

Doctors are just as busy as before vitamins

It isn't necessary to be a mind-reader to practice medicine, but it helps

The most hopeless patient is the gelatinous child of albuminous parents

The most ancient and the most modern vogue in medicine is psychotherapy

Gastroenterology might have succeeded earlier if its nomenclature had been patterned after the ponderous style of dermatology

A good surgeon is a physician who can operate but a good physician doesn't need to

We would understand nature if we understood the exceptions to the rules

Patients appreciate helpful suggestions more than health inventories

The findings of the Freudians are shocking if true,

JOHN D. D.
DECEMBER, 1943

to be a specialized course in general practice and he ought to leave college as well-fitted for his task as the man who intends to restrict himself to one phase of disease. His post-graduate work should be done not only in hospitals, but through apprenticeship to excel-

lent general men. His outlook would then be as specifically general as the other man's is generally specific. The public soon would learn, from employment of such a doctor, that they were dealing with an expert and one who could safely be trusted to refer when necessary.

Book reviews

Nervousness, Indigestion and Pain By Walter C. Alvarez, M.D. Harper and Bros., N. Y., 488 pp \$5.00 1943

The author started out to write a long-delayed new edition of his best-selling "Nervous Indigestion" but, as he says, before he got done he had an entirely new book with ten times as many words as were in "Nervous Indigestion" and so he gave it a new title.

He calls this a "different" type of book in that it deals more with sick, unhappy persons than with their diseases, more with symptoms and their meaning than with disease entities, more with the handling of patients than with the giving of medicines, and more with the puzzling, poorly understood and seldom described abdominal discomforts and indigestions than with the well-known organic diseases like ulcer and cancer and cholecystitis.

The book is different also in that it deals not only with those diseases which arise in the digestive tract and are described in the books on gastroenterology, but also with those many diseases such as constitutional inadequacy, psychopathy, the nervous breakdown, arthritis of the spine, migraine, and pelvic disease which the "stomach specialist" has to diagnose and struggle with day after day and many times a day.

As Alvarez says, if a gastro-enterologist is seeing such troubles every day then why shouldn't a book written to help him with his problems describe and discuss these troubles, even if they are not arising in any part of the digestive tract. So far as we know this is the first time in medical history that such a book has been written.

The book is different also in that in it the writer takes the reader with him into his office and there shows him so much of what every young practitioner wants to know, which is, how an internist's mind works as he tries to make a diagnosis, and what he says and is careful not to say as he talks to a fussy and difficult patient.

In this book the young physician is shown just how to take the type of history from which he can often make a correct diagnosis, and he is told what the many symptoms probably mean. The chapter on treatment will delight many physicians if only because in it they can learn the details of how psychotherapy is carried out.

The thousands of physicians who enjoyed "Nervous Indigestion" will probably enjoy this book too because it is written in the same human and chatty style, with a world of medical anecdote and much quiet humor along the way. Into this book Alvarez has poured much of the clinical wisdom he has picked up in thirty-three years of busy consultant practice.

In many ways it represents a graduate course in internal medicine.

Human Gastric Function An Experimental Study of a Man and his Stomach By Stewart Wolf and Harold G. Wolff. With a forward by Professor W. B. Cannon. pp 195, \$4.75. Oxford University Press, New York, 1943.

As indicated by the title, this is a study of gastric function in a 57 year old man with a fistula of the stomach. Gastrostomy was performed when he was 9 years old because of an oesophageal stricture resulting from drinking extremely hot clam chowder. During the ensuing 47 years he kept himself in a good nutritional state by feeding himself through the artificial opening. His defect did not interfere with performing hard work.

After the original operation a portion of the gastric mucosa had herniated and formed a permanent rosette-like collar around the stoma. The changes in the color of his collar reflected like changes in the mucosa within the stomach. This collar thus afforded an easily accessible view for studying the vascularity of the mucosa, as indicated by its changes in color, under various conditions. In addition to these circulatory changes, Wolf and Wolff investigated the motor and secretory activities of the stomach changes in the properties of the gastric juice under varying conditions, and carried out both gastroscopic and X-ray studies of the stomach.

Their findings make most interesting reading. They observed that increased secretion by the parietal cells was always accompanied by hyperemia of the gastric mucosa and that hyperemia also accompanied increased motor activity. When the mucosa was in a state of hyperemia and engorged it was unusually susceptible to injury and tended to hemorrhage under the slightest trauma. If the mucus layer were wiped from the mucosa and gastric juice allowed to come in contact with the denuded area, there resulted a further hyperemia and increased acid secretion. Prolonged contact of the denuded mucosa with the gastric juice, together with a minor erosion, resulted in the formation of a peptic ulcer.

A number of physical and chemical stimuli were applied to the gastric mucosa with interesting results. Touch sensation was absent but pressure sensation was present and roughly localized. Temperature sensation was absent between 18° and 40° C but present beyond this range. The important observation was made that although painful sensations could not be elicited by stimulating the normal gastric mucosa minor stimuli caused pain when the mucosa was in-

flamed and oedematous

The effects of various drugs (lustramine, mechoyl, atropine, epinephrine) were studied. The influence of these agents on the secretory and motor activity of the stomach depended in a large degree on the previous emotional state of the subject. It is interesting to note that no effects from smoking tobacco were observed.

The portion of the book dealing with changes in gastric function accompanying various emotional states of the subject make most interesting reading. The emotion of fear was accompanied by a depression in gastric function but the emotions involving frustration and repressed conflict were accompanied by an increase in the vascularity of the secretory and motor activities. The stomach mucosa under these conditions became red, swollen and turgid, and resembled strongly the hypertrophic gastritis familiar to the gastroscopist.

The authors are to be commended for taking full advantage of their opportunity to make a thorough study. This book is a "must" for anyone interested in gastroenterology.

The Triumphant Spirit,—A Study In Depression
By E. Graham Howe, pp. 344, Faber and Faber, London, England, 8 shillings, 6 pence

Howe is a successful London psychiatrist who lines up with Jung and takes an intuitive approach to the subject of depression, as well as to the ambitious problem of what ails the world. He believes that the supremacy of the spirit, the importance of the individual and a better agriculture are the three "musts" for a better world after the war. The major assumption of the book is to the effect that a close study of individuals reveals not only why they may present depression, but by inference, it reveals also why the whole of mankind has slipped. A number of case histories are presented to show why individuals have nervous breakdowns and among the crises are,—refusal to admit or accept the facts of life, an insistence that the world must be perfect, maintenance of a moralistic attitude, being too 'high-minded' neglecting the biological side of one's nature, getting in too much of a rut, insistence upon happiness, failure to put high ideals into action. The author steers clear of definitions and maintains a growing attitude of mind himself. His books are his patients. He uses formal diagrams which no doubt are useful to certain types of readers in impressing his points upon them. In places this book attains the grandeur of a classical essay. His references to the psychological reactions of Britons at war is splendid writing. No one who has read the seven books by Howe can doubt that he represents something new and something which is at times puzzling in the domain of psychology. Possibly his chief contribution consists in his advice to people to accept life as they find it to accept sorrow reverses, even sin, without attempting to deny any por-

tion of experience. He is an idealist and at the same time an extreme realist. At any rate, his admission that the human experience rightly includes a spiritual element, which is just as real,—though not more real—than the biological element, is an attitude which will shock no one except the completely materialistic and formalistic disciples of the unhappy era of mechanism, which managed to produce its own psychology. One might almost wish that Howe sometime would write a pure philosophy. At present, however, it is obvious that his chief interest is healing. In this domain, his originality is refreshing and promises to make deep impression upon formal psychiatry if he lives long enough.

Urine and Urinalysis By Louis Gershenfeld Philadelphia, Lea and Febinger Second Edit., 304 pp., 1943 (\$3.25)

Completely revised from an earlier edition, this book is destined to have an important place in the physician's library and the clinical laboratory. The procedures for carrying out various kidney function tests, the methods of chemical, physical and microscopic urine analysis, and the significance of the various findings are thoroughly discussed. An appendix giving instructions for the preparation of reagents and describing methods and apparatus which are used only on occasion completes the volume. Forty-two figures are included. A useful book and heartily recommended.

Physiology of the Nervous System By John T. Fulton New York Oxford University Press Second Edit., 614 pp., 1943 (\$9.00)

The first edition of this book by Professor Fulton was reviewed in this Journal in the issue of December, 1939. At that time it was said that "this book is a splendid book and one that is much needed today." This statement still applies to the second edition. The book has been revised to include many of the recent developments in the field of neurophysiology. The consequences of various brain and cord injuries, such as may be experienced in war are noted. The chapter on conditioned reflexes contributed by Dr. H. S. Liddell of Cornell University, emphasizes to a nice degree the complex physiological integrations which are concerned in even our simplest everyday habits. Of special interest to the gastroenterologist are the chapters on the autonomic nervous system and the hypothalamus. One must be familiar with the physiology of the autonomic nervous system and centers of integration of the higher vegetative functions to really understand the coordinating functions of the visceral organs.

Each chapter has a brief summary of its context. This book is both a text and reference volume. Sixty-six pages closely packed with references make it a valuable source-book to neurophysiological literature.

Abstracts of Current Literature

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

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B C RIGGS

FREDERICK H SCHARLES
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I M THEONE
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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

ROBINSON, D W AND HARLESS, M S *Papillary cystadenoma lymphomatosum of the parotid gland (Surg Gyn Obst, V 76, P 449, 1943)*

The authors collected from the literature 67 cases of parotid gland cystadenoma and add 4 cases of their own. In only two of the 67 cases reported were there signs of malignant changes. In their own cases the growths were benign and composed of numerous cystic spaces which were lined with well-differentiated columnar epithelium. Within the delicate reticulum of the stroma were numerous pockets of closely packed lymphocytes. The histology of the tumor is figured—N N Underhill

ALLISON, P R *Specimen of ante-thoracic oesophagus (Proc Royal Soc London, 36, 342, May 1943)*

The oesophagus and upper part of stomach had been removed for carcinoma of the abdominal oesophagus. An ante-thoracic oesophagus was constructed. The patient died a year later of secondary deposits. A peptic ulcer was found at the junction of the skin and gastric mucous membrane. During life the patient complained of some pain in this area—N N Underhill

STOMACH

HEBBEL, R *Chronic gastritis, its relation to gastric and duodenal ulcer and to gastric carcinoma (Am J Path, V 19, P 43, 1943)*

Studies were carried out on 260 stomachs obtained at autopsy and 158 stomachs obtained by operation for ulcer (106 cases) or carcinoma (52 cases). An attempt was made to correlate gastric carcinoma with gastritis. The results, however, do not support the view held by some that carcinoma arises more frequently in a stomach which already has an existing diffuse gastritis—I M Theone

BOWEL

CALDWELL, W A AND HARDWICK, S W *Observations on Flexner dysentery (Edinburgh Med J, V 50, P 129, March, 1943)*

An account is given of an institutional outbreak of Flexner dysentery which occurred in the mid-winter

and early spring months. A careful routine was adopted for the collection of fecal specimens. Specimens which had been in glycerine-saline several hours gave better results than the rectal swab method, and desoxycholate-citrate medium was preferred to MacConkey's. Most of the cases were mild, with the mortality rate being under 4%. The majority were treated by the sodium sulfate method. Of the cases in which sulfaguanidine was tried, the best response was obtained with the early ones. In an effort to prevent spread of the infection a vaccine was tried. The immunity conferred, if any, was of very short duration, yet prophylactic inoculation is recommended in a ward if given immediately following the occurrence of one or two sporadic cases. Emphasis was placed on the following factors important in the spread of the disease: (1) failure of the nursing staff from ignorance or from a mistaken sense of duty to report gastro-intestinal symptoms; (2) the common temporary carrier state following infection; (3) the occurrence of "missed" cases—G P Blundell

SCHATTLEFIELD, L E *Lipomas of the gastrointestinal tract (Surgery V 14, P 47, July, 1943)*

This extensive review of the literature of lipomas of the gastrointestinal tract begins with the earliest reported case (Morel in 1876). More than one-half of all lipomas of the gastrointestinal tract are found in the small intestine and about one-third are found in the ileum. Over one-third of all cases result in intussusception.

The tumors may be either subserous or submucous. The symptoms of such tumors are those symptoms that might result from the mere presence of a tumor, such as obstruction and intussusception, or those symptoms which might arise from complications, that is, hemorrhage, etc. Symptoms may be entirely absent. The diagnosis of these tumors is rarely made as there are no diagnostic signs. An attempt is made by the author to present definite clinical manifestations which lipomas of the intestinal tract produce together with the symptoms of each type. The treatment of these lipomas is that of removal of the tumor with that section of the intestine necessary.

The paper is an excellent review of the subject and has an extensive bibliography—Adolph A Walkling

ROSS, J. T. *The significance of rectal bleeding* (New York State J Med, V 43, P 763, Aug 1943)

Anoscopic, rectoscopic, palpatory and roentgenographic examinations should always be done to establish for certain that rectal bleeding is due to hemorrhoids and not malignancy. Of the ulcerative diseases of the rectum the most important are lymphogranuloma venereum, chronic ulcerative colitis, the dysenteries and tuberculosis. The most serious causes of rectal bleeding are carcinoma and chronic idiopathic ulcerative colitis.

Hemorrhagic diseases and intussusception are the most common causes of rectal bleeding in the infant, prolapse, polyps, pin worms and acute gastroenteritis in children, and hemorrhoids fissure fistula ulcerations, dysenteries, and polyps in the 20 to 40 year old group. In older patients carcinoma, impaction and prolapse are additional causes for rectal bleeding.—I. M. Theone

LAMSON, O. F. *Appliance for colostomy control* (West J Surg, V 51, P 127, 1943)

Lamson describes a removable plug which is useful in colostomy to prevent leakage. The appliance consists of a disc, somewhat larger than the stoma, with a small balloon attached. The balloon is inserted into the colon and gently inflated. The pressure of the balloon keeps the disc firmly against the stoma and prevents leakage. A valve in the disc controls inflation and deflation. The balloon is deflated and withdrawn when evacuation is desired. The appliance should be used only some time after operation and in the absence of any colostomy infection.—D. A. Woch-en

SCHNEPP, K. H. *Diaphragmatic hernia as a cause of "intractable heartburn" of pregnancy* (Amer J Obst Gyn, V 46, P 142, July, 1943)

Schnepp states that "diaphragmatic hernia can cause symptoms resembling those caused by peptic ulcer or gall bladder pathology. Under conditions of general practice symptoms to bring the patient to the roentgenologist for examination will reveal diaphragmatic hernia in about 2 out of 100 patients. One would expect such symptoms in particular to be precipitated during the stress and strain of labor. The author concludes from his study that "intractable heartburn" of pregnancy, appearing after the 12th week, not relieved by usual medications and usually aggravated by the recumbent position, may well constitute the rarely recognized symptoms of diaphragmatic hernia.—N. N. Underhill

CHARACHI, H. *Primary lymphosarcoma of the intestine in a boy of seven* (Am J Surg, V 59, P 601, 1943)

Nine years previously, when he was age 7, the subject had a resection of a lymphosarcoma of the ileum. The tumor had involved adjacent lymph nodes. In this follow-up study the boy was found to be in good

health and without symptoms. A search of the literature reveals that 404 cases of lymphosarcoma of the intestine have been reported. Of this number 103 were followed up carefully for a number of years. A survival of 5 years post-operative was shown by only 14 patients.—I. M. Theone

BLOCK, F. B. AND SALES, P. M. *Acute intestinal obstruction due to bands complicating pregnancy* (Am J Obst Gyn V 46 P 134, July, 1943)

The authors have reviewed the American literature of the past ten years of this all-important complication of pregnancy. Although not of frequent occurrence, they mentioned that the aim of their presentation was to direct attention to the serious combination of acute intestinal obstruction and pregnancy.

They have found only 13 cases reported during the past ten years. In 3 cases the mother died and in 3 cases the foetus was lost. Under the auspices of the Philadelphia County Medical Society a request was sent to 50 hospitals that a search be made through the records of the preceding 10 years. Thirty-three hospitals replied and those together with the cases obtained from the records of the County Medical Society yielded a total of 22 cases of intestinal obstruction complicating pregnancy. Of these 12 were antepartum. Of these 7 were due to bands of adhesions resulting from a previous operation. Death of the mother resulting in 5 cases and death of the foetus in 6 cases. The obstruction occurred between the third and seventh months in all except one case in which it occurred at term.

The authors report two cases that they had personally seen and who were operated immediately. In these cases the mother and child both came through all right.

In summarizing, the authors state that although acute intestinal obstruction is uncommon it is yet a serious complication of pregnancy. One of the most common causes of this complication is the presence of adhesive bands resulting from a previous lower abdominal operation which became taut as the enlarging uterus pushed the intestines into the upper abdomen. Obstruction may occur at any interval after an abdominal operation and the fact that a patient goes through a normal pregnancy after such an operation is no assurance that she will not become obstructed during a subsequent one.

During pregnancy mechanical obstruction should be suspected when there is a history of a previous lower abdominal operation, associated with the triad of cramp-like pains, vomiting, and obstipation. If x-ray examination reveals distended small bowel, the diagnosis is made, but negative x-ray findings do not rule out obstruction. Early operation is recommended to release the obstructing bands, and careful search should be made to release all points of obstruction.—J. Bernard Bernstine

GLABE, R A *Pain as a symptom in appendicitis* (*Minnesota Med*, V 26, P 622, July, 1943)

A brief review of the neuroanatomy of the region calls attention to the fact that there are two nerve supplies involved, the viscus innervation coming from the visceral afferent fibres of the splanchnic, and the peritoneal innervation from the somatic nerves. This explains the difference in sensation from the various parts of the bowel and peritoneum. The initial generalized pain arises from the appendix itself due to distension of the organ. This pain is only roughly localized to the viscus itself or is referred. The later localized pain arises from stimulation of the parietal peritoneum by the spreading inflammatory process. With the involvement of the peritoneal serous covering and parietal peritoneum, localization of pain, skin hyperesthesia, rigidity, fever and leucocytosis are manifested. The difficulty of making a diagnosis in the retroperitoneal, retrocecal and retrocolic types is due to the fact that the sensitive peritoneum is not so readily situated. The localizing pain may be entirely absent and the rigidity and tenderness may be in the right lumbar region. The importance of bimanual or rectal examination cannot be overemphasized.—H N Metzger

GFRWIL W H JR AND STONE, H B *Enteric intussusception in adults* (*Surg Gyn Obst*, V 76, P. 95 Jan 1943)

An interesting and unusual case of adult enteric intussusception with polyposis of both the small and large intestine is reported. The rarity of these two conditions is stressed and the diagnosis by means of double contrast barium enema x-ray visualization of the colon is emphasized.

Intussusception is defined as the invagination of one part of the intestine into another part. An anatomic and an etiologic classification is given. In the latter, there are two types, the primary, which occurs usually in infants and the secondary form in adults, which follows some organic causative factor. The mechanism of the secondary type is described as being that of spasm of the intestinal wall below the organic lesion, and relaxation of the portion terminal to the spasm. This condition favors the reception of the contracted portion into the dilated portion. The mechanism in babies may be the same and follow inflammation of the lymphoid tissue in the lower ileum. The causes of the secondary type mentioned were benign and malignant neoplasms, Meckel's diverticulum, gumma, ulcers of dysentery, typhoid and tuberculosis, enterocysts and parasites. In cases of adult intussusception, careful search for organic lesions was advised.

In the infant the symptoms are typical and the treatment is surgery unless it is promptly reduced by an enema. Resection is not usually necessary and reduction alone usually leads to a cure without recurrence. The symptomatology of the adult form is varied and usually comes to surgery with the diagnosis of intestinal obstruction. A careful search for the cause and its removal are important in treatment.—J T McGeehan

PANCREAS

DE COURCY, J L *Dermoid cyst of pancreas* (*Ann Surg*, V 118, P 394, Sept 1943)

A search of the literature to date has revealed only two cases reported with dermoid cyst of the pancreas. In this, the third case to be described, the cyst occurred in a 2 year old infant. Surgical treatment was successful. The symptoms were obscure and diagnosis difficult.—D A Wochen

LURIE T A AND LEVY, SOL *Pancreatic encephalopathy. A review of the literature, with report of a case* (*Am J Dis Child*, V 66, P 49, July, 1943)

Studies on encephalopathies resulting from somatic illnesses, and which were previously thought to be associated encephalitis, are discussed. Particular mention is made of the suggestion of Wechsler that avitaminoses produced the alcoholic encephalopathies, and this is tied up with the report of Rothermich and von Haam on psychosis with pancreatic changes. In the authors' case, the patient was a 14 year old girl who presented a typical history of normal health until the age of six years. She then began to have recurrent attacks of pain in her abdomen, with nausea, vomiting, and loss of appetite. In the past three months eating became very erratic. The patient was poorly nourished and showed several psychotic and neurologic manifestations typical of the condition. After treatment with only well-balanced and vitamin-fortified meals, she recovered completely within three months.—Wm D Beamer

LIVER AND GALLBLADDER

SHEINFELD, W I AND MACKLER, H *Gallstone ileus. Pyloric obstruction caused by gallstone* (*Am J Surg*, V 61, P 439, Sept 1943)

A case of a large gallstone which had become impacted in the pylorus and extended into the stomach is presented. The calculus was removed by incision through the stomach and a chronically diseased, cicatrized gall bladder was removed at the same time. This necessitated a closure of a fistulous tract between the gall bladder and the gastroduodenal junction. The authors use the fatal outcome on this case on the first postoperative day to call attention to the need for early recognition of intestinal obstruction due to gall stones. They suggest that the symptomatology follows a definite pattern and that several diagnostic x-ray methods properly used will aid in early discovery of the condition.—Wm D Beamer

YARDUMIAN, K Y AND WEISBAND, B J *The cephalin cholesterol flocculation test in liver disease* (*Am J Clin Path*, 13, 383, August, 1943)

Cephalin cholesterol flocculation tests were carried out on the serums of 49 patients with clinical evidence of hepatobiliary disease and of 156 unselected patients as controls. Other liver function tests and frequently a laparotomy and biopsy of the liver were done as a

chick False positive reactions were seldom encountered. When it was positive in jaundice, there was attending parenchymatous damage. In cirrhosis the results are very irregular, ranging from negative to strongly positive. A constantly positive test indicates the probability of permanent damage. A progressively weaker reaction indicates recovery. Thus the cephalin cholesterol flocculation test is of value as a prognostic aid. The test is sensitive and should be done in conjunction with other recognized liver function studies. The preparation and technique are described.—Wm D Beamer

BOLES, R S *Alcohol and cirrhosis of the liver (Southern Med J, V 36, P 353, May, 1943)*

The etiology of the disease described as hepatic cirrhosis still remains unknown. Animal experiments attempting to reproduce the clinical condition have been, on the whole, disappointing. Dogs fed alcohol develop fatty livers but the fat deposition disappears when the alcohol is withdrawn. Dogs develop hepatic cirrhosis best when the alcohol feedings are combined with a protein-vitamin B deficient diet. Of 4,000 autopsies reported by Boles, 6 per cent showed some evidence of liver cirrhosis. Of this number 62 per cent could be classified as "alcoholic cirrhosis," although two-thirds of these patients had no history of excessive alcohol consumption.

Boles concludes that alcohol alone does not cause liver cirrhosis but that under certain conditions of diet (or other factors) it may contribute to its development.—F. X Chockley

ULCER

ALVAREZ, W C *Benign peptic ulcers coming repeatedly in a leather bottle stomach. Case report (Proc Staff Meet Mayo Clinic, 18, 298, Aug 1943)*

A man with a duodenal ulcer of long standing was found at operation to also have a leather bottle type of stomach with an ulcer on the posterior wall near the cardia. The gastric ulcer was malignant, and a partial resection and gastroenterostomy was done. Two years later the patient returned with a second malignant gastric ulcer, this time the ulcer was excised. The patient lived another two years. Throughout the four years after the first operation the patient remained well and gained weight although it is known that the stomach was highly infiltrated with malignant cancer cells.—D. A. Wachen

SMITH, L A AND RIVERS A B *Gastroileostomy and gastroileal ulcer (Surg Gyn Obst, V 76, P 110 Jan. 1943)*

The authors report 8 cases of gastroileostomy. They state that this condition must be considered among the possible causes of symptoms occurring after gastroenterostomy. This type of anastomosis occurs as a result of a surgical error, and the symptoms depend chiefly on the location of the anastomosis and on whether or not ulceration is present. In a few of these cases the stoma was located only a few inches from

the ileocecal valve. In 3 of the cases gastroileal ulcer was present.

The chief symptoms are diarrhea, vomiting, loss of weight and pain. The diarrhea typically began soon after operation and was henteric in type. Vomiting occasionally had a fecal quality. The weight loss varied with the severity of diarrhea. The pain in some cases was of the bowel type, but with the presence of gastroileal ulcer it resembled that of gastrojejunal ulcer. Ulcers were present only when the concentration of free acid in the stomach was significant. Other complications noted were nutritional deficiencies, nutritional edema, hypoproteinemia and multiple neuritis.

The treatment of gastroileal stoma is surgical, disconnection of the abnormal anastomosis, excision of any gastroileal ulcer, and gastrojejunostomy (if the duodenum is normal) or partial gastrectomy may be performed.—John T McGeehan

THERAPEUTICS

GILCHRIST, R K AND OTHERS *Traumatic peritonitis. Choice of routes for administration of sulfonamides (Surg Gyn and Obst V 76, P 689, June, 1943)*

This investigation was carried out by R K Gilchrist, F H Straus, R. Hanselman, C C Sroa, S E Lawton and M Freeland. These workers found that sodium sulfathiazole when given by vein reaches adequate concentration in the blood and peritoneal fluid in about fifteen to thirty minutes. The recommended dose is one-half gram per 10 pounds body weight followed by intravenous administration of plasma, blood, etc. The blood and peritoneal fluid levels must be maintained by repeated sulfathiazole administration.

A superior mode of administration appears to be that of direct injection into the peritoneal cavity. If the sulfonamide is relatively insoluble (such as sulfathiazole) adequate concentrations are reached rapidly and maintained for about twenty-four hours. The authors observed no peritoneal reactions or phlebitis attributable to the use of sulfonamides.—G Klenner

SURGERY

RANKIN, L M AND EGER, S A. *Intestinal obstruction due to gallstone (Am J Surg, 61, 445, Sept 1943)*

Three cases of gallstone obstructing the intestinal tract (two the jejunum and one the ileocecal junction) are reported. Each patient was an obese female, aged seventy-seven, fifty-nine, and seventy-two years respectively. The authors recommend expressing the stone to another and healthier portion of the tract before removal and used this method in these cases. The gall bladder was not disturbed in any case, although there were adhesions about each. One patient developed cardiac failure on the ninth postoperative day and expired on the thirteenth. The other two had normal convalescence and no recurrence of symptoms. Snyder is quoted as stating that the expected mortality attending surgical intervention is between 60 and 70 per cent.—Wm D Beamer

MASSON, J. C. AND JUDD, E. S. *Acute intussusception: fixation of cecum by exteriorization of appendix* (Proc. Staff Meet. Mayo Clinic, 18, 333, Sept. 1943)

Eleven infants, five males and six females, with intussusception were operated on. The ages ranged from 3 to 12 months and duration of symptoms from 8 hours to 5 days. All presented the classical symptoms. Nine of the patients survived the operation and only two died very soon after.

The affected area is approached through the usual incision and the intussusception reduced by gentle milking from the distal aspect toward the proximal. Traction on the proximal loop is always avoided. The meso-appendix is clamped, divided and ligated and the freed appendix is then brought through a small stab wound just medial to the anterior spine of the ileum. The cecum must be flush against the parietal peritoneum, one or two stay sutures may be employed for anchorage. The rim of the meso-appendix remaining attached to the base of the appendix is sutured to the skin. The wound is closed in the usual manner. The appendix begins to drop away after two to four days. By the eighth to tenth day only a mucous fistula remains which presents no complication.

Excellent results were realized in 8 of the 9 surviving patients, the other patient had a recurrence which required the same procedure, using the cord-like appendiceal stump for exteriorization. Since the operations, from 5 months to 18 years have elapsed and all have been free from symptoms.—D. A. Wochen

EXPERIMENTAL MEDICINE

SECRETION

ADAMS, W. L., WELCH, C. S. AND CLARK, B. B. *The effect of sodium bicarbonate on gastric secretion* (Am. J. Physiol., V 139, P 356, July, 1943)

The controversial effect of NaHCO_3 administered by mouth on gastric secretion and the concept of a "rebound" or "secondary" secretion of acid are fully discussed. In order to approach actual physiological conditions as closely as possible while allowing continuous observations, the authors have been apparently the first to experimentally use the Cope gastric pouch. Their technique and procedures are described in detail.

Five Cope pouch dogs were used. The experiment was divided into three series. In the first and second series, dogs were given 1.5% and 2% NaHCO_3 in 50 cc doses, by stomach tube, three times daily, and in the third series 4% NaHCO_3 was allowed to remain in direct contact with the pouch mucosa for three weeks. In all the series, the volume secreted during the first nine hours showed increases up to 38% with parallel chloride changes, while, during the remainder of the day, decreases ranged from 88% to 61% in volume and up to 37% in chloride. The net results for twenty-four hours were insignificant changes to marked increases as compared with test-meal control studies done previously. Further changes were observed in the net decreases up to 38% in the total base and marked increases to 62% in the free acid. Thus in these experiments the NaHCO_3 elicits a higher percent-

age of the total chloride as free acid which meets the need of more free acid to neutralize the NaHCO_3 . There was no significant change in the hematology of these animals and the usual reciprocal relationship between plasma chloride and carbon dioxide capacity during NaHCO_3 feeding was observed.

It is the belief of the authors that neither fractional gastric analysis nor pouch studies for a few hours following a test meal provides adequate data to reveal the effect produced by NaHCO_3 . (1) the amount of acid shows at least two factors contributing to the "rebound" effect produced by NaHCO_3 . (1) the amount of acid secreted is increased and (2) a shift occurs in secretory activity to greater amounts at earlier periods after a test meal. The role of these factors in "rebound" gastric acid secretion as seen in fractional gastric analysis is further discussed.—H. Siplet

MOTILITY

HEDARY, GIDEON, SOMMLER, HUGO H. AND GONCE, JOHN D. JR. (University Wisconsin). *Comparison between stomach and colonic emptying times of Pasteurized, chocolate, and evaporated milk* (Milk Dealer, V 32, pp 26-28, 58, 60, 64, 66, 1943)

In order to determine the comparative ease of digestion of the 3 milks used, experiments were conducted using 10 normal, healthy children with no indications of digestive disorders. BaSO_4 was added to the milks in the proportion of 1:4 and the progress of the milk through the digestive tract was followed by means of roentgenograms. No other food was taken during the experiment. The evaporated and chocolate milks were of the soft curd type, and the unmodified whole milk, used as a control was a hard curd milk. Roentgenograms were made at intervals of 2, 4, 5, 6 and 24 hours after ingestion of the milks. No difference was noted in the stomach and colonic emptying times of the 3 milks.—J. L. Hileman (Biological Abstracts)

LEWIS, JULIA H. AND SARBIN, THEODORE R. *Studies in psychosomatics I. The influence of hypnotic stimulation on gastric hunger contractions* (Psychosom. Med. V 5, P 125, 1943)

The usual method of having the subject swallow a balloon was employed. To the balloon was attached a flexible rubber tube which in turn was connected to a chloroform manometer. Experiments were performed on 8 normal subjects to determine the influence of hypnotic stimulation on gastric hunger contractions. It was observed that if a fictitious meal is given by hypnotic suggestion results are obtained similar to those seen in a hungry person in the waking state who partakes of real food in that the gastric hunger contractions are inhibited and feeling of satiation is evoked. The gastric hunger contractions are inhibited by fictitious feeding most frequently in the deeply hypnotized subjects less frequently in the moderately hypnotized subjects and not at all in the non-hypnotized subjects. No amount of hypnotic suggestion could produce anything resembling the hunger rhythm.—Felix Deutsch (Biological Abstracts)

PATHOLOGY

DRIVER, R. L., DOZIER, G. S. AND DENHAM, H. C. *Effect of various chemical agents affecting permeability of the mucosa on the formation of ulcers* (Science, V 98, P 158, August 13, 1943)

In dogs under anesthesia, loops of jejunum were perfused with various solutions. Neither solutions of pepsin (2 per cent) nor of HCl (0.1 N) produced ulcers when perfused alone, however, when the loop was perfused with pepsin and acid the percentage occurrence of ulcers was 27.3 per cent. This incidence of ulcer formation was increased greatly by the addition to the acid-pepsin solution of substances which lower surface tension. Ulcers occurred in 50 per cent of the loops with methyl salicylate added, 53 per cent with hexyl-resorcinol, 69.2 per cent with sodium hexametaphosphate, and 71.4 per cent with tetramethyl glycol. The ulcers were not due to differences in pH of the solutions. The authors conclude that "substances which increase the permeability of intestinal mucosa by a lowering of surface tension or other means facilitate the formation of ulcers"—M. H. F. Friedman

LAUFMAN, H. *Gradual occlusion of mesenteric vessels: an experimental study* (Surgery, V 13, P 406, March, 1943)

The author produced gradual occlusion of the mesentery artery in three of six experimental animals and occlusion of the mesentery vein in two out of five experimental animals. Studies were made to determine the effect on the intestine and the general condition of the animal.

Dupont cellophane was used by wrapping four folded layers loosely about the vessel. The ends were sutured with silk mattress stitch so that the cellophane hugged the vessel snugly, but did not constrict. Animals with the superior mesenteric artery so treated became progressively thinner and lost their appetites. Those animals in which the superior mesenteric vein was wrapped with cellophane at no time showed any ill effects. There was a severe degree of tissue irritation caused by the cellophane and in those animals in which the artery had been completely occluded the intestinal wall appeared pale and thin. There was no infarction. The small subserosal vessels contained thrombi. The same changes occurred in all three animals in which gradual occlusion was complete. There were no changes in the intestinal walls of the animals in which the artery occlusion was incomplete. Gradual occlusion of the superior mesenteric vein resulted in no lesions of the intestine.

The collateral venous drainage of the intestine was established between the small vessels about the kidney and the parietal peritoneum. A photograph accompanying the article shows this very clearly. This finding explains the lack of symptoms in man in gradual occlusion of mesentery veins—Adolph A. Walking

HANDLER, P. AND BERNHEIM, F. *The effect of choline deficiency on the fat content of regenerated liver* (J. Biol. Chem., V 148, P 649, June, 1943)

The authors call attention to evidence which suggests that fatty livers are induced by choline deficiency only when all other dietary factors are close to optimal for growth. Experiments were conducted on partially (to 80 per cent), hepatectomized rats in order to determine whether the limiting factor is the metabolism and growth of the liver alone or of the entire body. Liver regeneration in partially hepatectomized rats proceeded rapidly when the animals were maintained on diets deficient in choline alone or both choline and thiamine. Liver regeneration was obtained even in animals whose total body weight was depressed by excessive amounts of nicotinamide in the diet. The regenerated livers of choline-deficient animals showed the usual fatty infiltration when the total body weights were maintained or increased. The fat content of the regenerated livers of choline-deficient rats was slightly below normal in those animals whose total growth was depressed by thiamine deficiency or by ingestion of excessive amounts of nicotinamide. It is suggested that the development of fatty livers in rats in choline deficiency can proceed only when all other dietary factors will permit the growth of the entire animal rather than merely growth of the liver—J. Logan Irvin.

SHIMKIN, M. B., ZON, L. AND CRIGLER, C. W. *Blood histamine in gastric cancer and peptic ulcer* (Proc. Soc. Exper. Biol. Med., V 52, P 335, April, 1943)

Blood samples were taken from adult male patients with gastric cancer, gastric ulcer, or duodenal ulcer. Diagnosis was established either at subsequent operation or on the basis of roentgenologic findings. Hodgkin's disease, leukemia and polycythemia vera were also studied.

The normal blood histamine has been reported in the literature as ranging between 1.8 and 7.8 gamma per cent (average 4.0 gamma). The authors found their gastric carcinoma and peptic ulcer patients to have a blood histamine which was essentially normal in concentration (1.2 to 8.5 gamma per cent). There was found no correlation between blood histamine level and the presence or absence of free hydrochloric acid in the stomach. Some very interesting observations on the blood histamine in polycythemia and leukemia are reported also—M. H. F. Friedman

METABOLISM AND NUTRITION

SCHOL, A. T. *Nitrogen storage following intravenous and oral administration of casein hydrolysate to infants with acute gastro-intestinal disturbance* (J. Clin. Invest., V 22, P 257, March, 1943)

The subjects of the study were twenty male infants ranging in age from 2 weeks to 8 months and in weight from 2.6 to 9 kilograms. Dehydration and acidosis were evident and the gastro-intestinal disorders were severe enough to foreclude feeding by mouth. Intrave-

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ous saline was given for dehydration and glucoselactate for the acidosis. Nitrogen was supplied by intravenous administration of a commercial casein hydrolysate. Specific drugs and blood transfusions were given when indicated.

Treatment was in three phases: (1) no food by mouth and casein hydrolysate intravenously until vomiting and diarrhea stopped, (2) the same solution as above orally instead of, or with, intravenous use, (3) oral casein food and (or) milk formulae given when the solution in phase 2 was tolerated.

Four controls were used, two receiving glucose and saline intravenously and two milk formulae by mouth. Nitrogen in the food, urine, and feces were determined by micro-Kjeldahl technique and the nitrogen expressed as grams per 24 hours and as grams per kilogram body weight.

Edema was the only complication due to the therapy. This was overcome by cutting down the NaCl intake and the time of injection. Two infants died of pre-existing disease other than the gastro-intestinal disorder.

All infants receiving casein hydrolysate showed positive nitrogen balances while the controls were all in negative nitrogen balance. Nitrogen output in the feces was roughly 2 to 7% of the dry weight and this held true of diarrheal and normal stool of the infants fed parenterally or orally, and whether given casein hydrolysate or milk. Nitrogen retention was correlated with intake. It rose with increased intake but not by a constant factor. The average intake to maintain equilibrium was 0.35 gm per kilogram equaling about 2 to 8 gm of casein hydrolysate. Clinically the minimum intake of use is 0.4-0.5 gm per kilogram. With the highest intakes nitrogen balances were higher in proportion and amount than expected for well infants. Weight gains were dependent only on the state of hydration. Fever had no apparent effect on the nitrogen balances. Nitrogen retention levels were approximately the same at the same levels of intake regardless of the route of administration or the phase of the disease.—T. A. Tice

REFERS, P. E. ABELS, J. C. AND RHODES, C. P.
Metabolic studies in patients with gastro-intestinal cancer IV. Fat metabolism. A Method of study (J. Clin. Invest., 22, P. 243, March 1943)

The authors describe a method of investigating the ability of patients with gastro-intestinal cancer to digest and absorb fats and the results of its application to patients with various disorders.

The method of determining the ability to digest fats was a simple one. It consisted of giving each patient a diet containing approximately 15 gm of protein, 15 gm of fat and 30 gm of carbohydrate per kg. of body weight, and measuring by the Van Slyke method of fat determination the amount of fat excreted in the stool. Then after a few days on this basal diet, the patient was given a supplemental fat diet in order to obtain a measure of the individual's ability to absorb fat at both a normal and high level of fat ingestion. The results of the method were checked by the method of

fat determination of Bloor and found to be reasonably close to be considered valid.

The findings in the patients studied are as follows: (a) Two individuals with normal gastro-intestinal tracts were found to be able to absorb 96% and 97% respectively of the normal diet, and 92% of the additional fat load. The fat output dropped to normal in 48 hours. Therefore the fat load does not decrease significantly the ability to absorb fat from the intestinal tract. (b) This group included three individuals, one with gastric carcinoma, a second who had undergone complete gastrectomy 20 months previously and a third with atrophic gastritis. The patient with gastric cancer absorbed 89 to 95% of the normal diet and 93% of the supplement. Thus the addition of this fat did not decrease the efficiency of absorption. The patient with total gastrectomy absorbed 20 to 34% of the normal diet and only 10% of the supplementary fat. This indicated not only that the patient had considerable steatorrhea on a low fat diet but also that the addition of the fat load significantly increased the fat loss. The question arose as to the relationship of the absence of gastric mucosa and the occurrence of steatorrhea, so the following patient was studied. The patient with atrophic gastritis retained 80 to 90% of the ingested fat and 78% of the increased fat load. The absence of normal gastric mucosa may have the same effect on the ability to absorb fat. (c) This group consisted of two patients with hepatic cirrhosis. The absorption of fat on the low fat diet was 92 to 98%. The patients were able to absorb 93 to 97% of the supplemental fat load. Thus no significant defect appeared to exist in the absorption of fat from the gastro-intestinal tract of patients with hepatic cirrhosis.—J. T. McGeehan

MISCELLANEOUS

KALK, H. *Laparoscopy* (Deutsch. Med. Wochenschr., V. 68, P. 677, 1942)

Many diagnostic applications of laparoscopy are discussed. Excellent, laparoscopic photographs of various conditions of the appendix, liver, gallbladder and intestines, including carcinoma, are presented.—(Courtsey Biological Abstracts)

TILLISCH, J. H., STATLER, J. F. AND LOVELACE, W. R. *Study of the effects of airplane transportation of 200 patients* (J. Aviation Med., V. 14, P. 162, Aug. 1943)

The study was made on 200 patients who were transported by air. Mild discomfort from flying was experienced by 69 per cent of the cases. Of extreme interest was the observation that patients who were recovering from abdominal operations or who suffered from perforated gastric or duodenal ulcers were prone to suffer ill effects. It is believed that the expansion at high altitudes of gas normally present in the gastro-intestinal tract may rupture healing tissue. Fecal material may thus be forced by the expanding gas into the peritoneal cavity. Patients with acute appendicitis, strangulated hernia, intestinal obstruction, ulcers, and those recently operated on therefore should not be transported by air unless absolutely necessary.—M. H. Friedman

The Newer Concepts of Meat in Nutrition

Meat . . .

and the Patient's Speedier Return to Productivity

THE need for man power in all types of industry makes it imperative that the incidence of illness be held to a minimum, and that convalescence be shortened as much as possible. Both these objectives can be more readily achieved by maintaining a state of adequate nutrition.

During the period of recovery from surgery or infectious disease the return of strength and stamina is closely paralleled by metabolic readjustment of the organism. The increased protein requirement during this period is the reflection of a rebuilding and rehabilitation process, necessitated by the increased metabolic demands of temperature elevation and by re-

striction of food intake during the phase of acute illness.

The early inclusion of meat in the diet of the convalescent is an effective means of re-establishing nitrogen equilibrium. In addition to its biologically adequate protein, meat also provides significant amounts of the B vitamins and the minerals iron, copper, and phosphorus, all of which are needed in greater amounts during the period of convalescence.

The aroma of properly prepared meat arouses the appetite, and its extractives stimulate the flow of gastric juices, thereby increasing the desire for food and adding to the relish with which the meal is eaten.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



American Meat Institute
CHICAGO

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